Maternal Eating Disorders
Effects on Pregnancy, Infant and Child Development

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MATERNAL EATING DISORDERS: EFFECTS ON PREGNANCY, INFANT AND CHILD DEVELOPMENT

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Abstract

There is evidence that Eating Disorders (ED) may have implications for fertility, pregnancy and, diet and growth in their children. However, few large longitudinal investigations have been conducted. Women with ED have an increased risk for adverse obstetric outcomes; one proposed pathway is via elevated psychopathology during pregnancy, and consequently foetal overexposure to cortisol and corticotrophin-releasing-hormone, which may in turn have implications for stress regulation in their children.

The aim of this thesis was to investigate the effects of ED on fertility and pregnancy, as well as specific aspects of infant and child development.

Five interrelated studies were undertaken, utilising two separate methodological approaches. First, a large (n=12,254) longitudinal birth-cohort was employed to investigate fertility and attitudes towards pregnancy in women with and without ED, and longitudinal patterns of diet and growth in their children. Second, maternal psychopathology and cortisol levels during pregnancy, and potential associations with obstetric outcomes, were investigated in a clinical sample of women with and without ED (n=88). At eight weeks post-natal, infant cortisol levels in response to stress were investigated in a sub-sample of mother-infant dyads (n=59).

The findings suggest that women with ED take longer to conceive and more frequently experience negative feelings towards their pregnancy than women without ED. Women with active ED showed persistently high levels of psychopathology and differential diurnal cortisol patterns during pregnancy, which were associated with lower birth weights and shorter gestations. Furthermore, children of women with ED were found to experience elevated cortisol levels, and some differences in dietary patterns and growth trajectories.

The general strengths and limitations of these investigations are presented and areas for future research are considered. Finally, the clinical implications of this thesis are highlighted and suggestions are made for the treatment of women with ED during the pre-conception period, pregnancy and in the post-natal period.

Table Contents

List of Tables

List of Figures

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Common Abbreviations used throughout this Thesis

ED	Eating Disorder(s)
AN	Anorexia Nervosa
BN	Bulimia Nervosa
AN-R	Anorexia Nervosa – Restricting Subtype
AN-BP	Anorexia Nervosa – Binge-Purge Subtype
EDNOS	Eating Disorders not Otherwise Specified
BED	Binge Eating Disorder
SIV	Self-induced Vomiting
DSM	Diagnostic Statistical Manual of Mental Disorders
BMI	Body Mass Index (kg/m^2)
PI	Ponderal Index (kg/m^3)
HPA	Hypothalamic Pituitary Adrenal
CRH	Corticotrophin-Releasing Hormone
CAR	Cortisol Awakening Response
11 β-HDS2	11 Beta -hydroxysteroid dehydrogenase type 2
ALSPAC	Avon Longitudinal Study of Parents and Children
MoBa	Norwegian Mother and Baby Cohort Study
NEST-p	Nutrition Eating and Stress in Pregnancy (Study)
EDE-Q	Eating Disorder Examination Questionnaire
BDI	Becks Depression Inventory
STAI	Spielberger Trait-Strait Anxiety Inventory

PSS	Perceived Stress Scale
PRAQ-R	Pregnancy Related Anxiety Questionnaire (revised version)
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
OR	Odds Ratio
RRR	Relative Risk Ratio
CI	Confidence Interval
FFQ	Food Frequency Questionnaire
REF	General population (unexposed) reference group
s.d.	Standard Deviation
IQR	Inter-quartile Range
EDD	Estimated Due Date
SLaM	South London and Maudsley (NHS foundation Trust)
KCH	Kings College Hospital
KCL	Kings College London
NICE	National Institute of Clinical Excellence

Overview of Thesis and Candidates Contributions to Studies

Chapter One

Chapter one provides a contextual background to this thesis, and aims to outline the current literature on maternal eating disorders (ED) and identify the gaps in the evidence. The first section of this chapter provides an overview of ED, including diagnostic classification and epidemiology, followed by an introduction to the topic of parental psychiatric disorders. The second section provides an overview of the literature on ED in the pre-conception period, during pregnancy, and post-natal periods, as well as the implications for infant and child outcomes.

Chapter Two

This chapter provides an overview of the general aims of this thesis, generated from the literature review presented in the previous chapter, followed by a description of the general methodology used to address these aims. In order to investigate the specific aims of this thesis, two separate methodological approaches are utilised within two samples: the Avon Longitudinal study of Parents and Children (ALSPAC) and Nutrition and Stress in Pregnancy (NEST-p).

Chapter Three, Four and Five

Chapters three to five, provide the first three investigations undertaken in this thesis, which utilised data from ALSPAC. The investigation presented in Chapter Three aimed to examine fertility and feelings towards pregnancy in women with lifetime ED, compared to women without ED. The aim of Chapter Four was to explore different dietary patterns and macronutrient intake in children of women with ED, compared to children of women without ED, between the ages of three and nine years. Finally, Chapter Five aimed to determine whether growth trajectories (from birth until ten years) differ between children of women with ED or other psychiatric disorders, compared to children of women without ED.

These studies were developed and carried out by the candidate, under the supervision of Dr Nadia Micali and Professor Janet Treasure. The data used in these investigations were collected as part of ALSPAC, and prior to receiving the data it had been coded and entered by the ALSPAC team. The dietary patterns and macronutrient content analysed

within Chapter Four were obtained prior to the present thesis by Dr Kate Northstone and Dr Pauline Emmet, from Bristol University. The statistical analysis undertaken in Chapter Four was carried out in collaboration with Ms Ulrike Naumann (an expert Statistician in the Biostatistics department at the Institute of Psychiatry, King's College London) and growth models in Chapter Five were analysed with Laura Howe (an expert Epidemiologist and Statistician from the Bristol University).

Chapter Six and Seven

Chapter Seven and Eight describe the final two investigations undertaken in this thesis, carried out as part of the Nutrition and Stress in Pregnancy (NEST-p) study. The overall aims of these investigations were to examine maternal psychopathology (ED symptoms and behaviours, depression and anxiety) and stress (perceived stress and diurnal cortisol rhythms) during pregnancy and in the post-natal period, in women with active and remitted ED, compared to a healthy control group (Chapter Six). Potential associations with obstetric outcomes and, maternal psychopathology and stress during pregnancy were investigated in Chapter Seven. Furthermore, studies undertaken in Chapter Seven were aimed at determining infant stress response and cortisol levels at eight weeks post-natal in their infants.

These investigations were supervised by Dr Nadia Micali and Professor Janet Treasure. I was responsible for setting up this project, recruiting and assessing participants at all time-points. Parts of the data were collected by Emma Taborelli, Amanda Bye and Freya Corfield who are Research Assistants and PhD students at the Institute of Psychiatry, Kings College London and the Institute of Child Health, University College London. Biological analysis of salivary cortisol was carried out by Patricia Zunszain at the Laboratory of Stress, Psychiatry and Immunology (SPI-Lab), within the Institute of Psychiatry, Kings College London. All data analysis was carried out by the candidate under the supervision of Dr Nadia Micali.

Chapter Eight

This chapter provides a summary of the main findings from the investigations undertaken within this thesis, with reference to prior literature and the aims of the investigations. Following which, the key strengths and limitations are summarised, and

suggestions will be made for future research. Finally, the clinical implications of this research are considered.

Chapter 1. Literature Review

Parts of the chapter appear as articles in: British Journal of Obstetrics and Gynaecology and Minerva Psichiatrica.[1] [2]

1.1 Chapter overview

The aim of this literature review is to present a contextual background, outlining the current understanding of maternal eating disorders (ED) and identifying gaps in the literature. The first section of this chapter provides an overview of ED, including diagnostic classification and epidemiology, followed by an introduction to the topic of parental psychiatric disorders. The second section provides an overview of the literature on ED in the pre-conception period, during pregnancy, and post-natal periods, as well as the implications for infant and child outcomes. Given the breadth of the research area, this chapter will focus on the main maternal outcomes (fertility, pregnancy psychopathology and obstetric complications) and infant/child outcomes (stress reactivity, diet and growth) investigated within this thesis.

1.2 Introduction

1.2.1 Eating disorders diagnostic classification and epidemiology

ED are serious and enduring psychiatric illnesses, which can have a multitude of effects on the health and lives of sufferers. The fourth edition (text revision) of the Diagnostic Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 2000), currently classifies ED as three distinctive categories of disorder: anorexia nervosa (AN), bulimia nervosa (BN) and Eating Disorders not Otherwise Specified (EDNOS).

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[1] **Easter, A.,** Treasure, J., & Micali, N. (2011). Fertility and pre-natal attitudes towards pregnancy in women with eating disorders: results from the Avon Longitudinal Study of Parents and Children. *BJOG: An International Journal of Obstetrics & Gynaecology*.

[2] **Easter, A.,** Taborelli, E., & Micali, N. (2010). Obstetric outcomes amongst women with a history of anorexia nervosa. *Minerva Psichiatrica, 21*(3), 161-175.

Anorexia nervosa

According to the DSM, AN is characterised by the presence of four typical features: 1. a refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected); 2. an intense fear of gaining weight or becoming fat, even though underweight; 3. a disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight; and 4. in post-menarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. AN can be divided into two distinct subtypes: restricting type (AN-R) where the person has not regularly engaged in binge-eating or purging behaviour; and binge-eating/purging type (AN-BP) where the person has.

Bulimia nervosa

The main features of BN include recurrent binge eating combined with inappropriate compensatory behaviours, which must not occur exclusively during episodes of AN. Specifically, recurrent episodes of binge eating are characterized by both of the following: 1. eating, in a discrete period of time (e.g. within any two hour period), an amount of food that is definitely larger than most people would eat under similar circumstances; and 2. a sense of lack of control over eating during the episode (e.g. a feeling that one cannot stop eating or control what or how much one is eating).

In order for full criteria of BN to be met, binge eating (as defined above) must be combined with recurrent inappropriate compensatory behaviour to prevent weight gain, such as: self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting or excessive exercise. The binge eating and inappropriate compensatory behaviours must both occur, on average, at least twice a week on average for three months. Furthermore, self-evaluation is unduly influenced by body shape and weight. BN can be classified according to two distinctive subtypes: purging (BN-P) and non-purging (BN-NP) type.

Eating disorder not otherwise specified

EDNOS is a broad category of disorder that covers clinically significant ED, which do not meet full criteria for AN or BN. Examples presented in the DSM include:

1. For females, all of the criteria for AN are met except that the individual has regular menses.

2. All of the criteria for BN are met except that binge eating and inappropriate compensatory mechanisms occur at a frequency of less than twice a week or for a duration of less than three months.

3. recurrent episodes of binge eating in the absence of the regular use of inappropriate compensatory behaviors characteristic of bulimia nervosa, also classified as binge eating disorder (BED).

Given the more general definition of the EDNOS category, it is not surprising that a large proportion of individuals with ED are classified under this broad category. This is problematic since it is often overlooked in research, leading to fewer treatment guidelines for individuals within this category. Therefore, a primary goal of the forthcoming DSM-5 is to better define individuals who would currently meet criteria for EDNOS, and to determine if it would be more appropriate to reclassify them. Two main solutions have been proposed to achieve this. The first suggestion is to relax the classification of AN (e.g. removal of the amenorrhea criteria and/or rising of the weight threshold) and BN (e.g. lowering the binge eating and purging threshold frequency). Second, since it is thought that a large proportion of individuals who are classified within the EDNOS diagnosis meet criteria for BED, it has been proposed that BED should be removed from the EDNOS classification category and recognised as a third ED diagnostic category (American Psychiatric Association, 2010).

Transdiagnostic approach to classifying eating disorder

It is widely recognised that there is considerable overlap between the ED diagnostic classifications defined above, and it is not unusual for individuals to meet diagnostic criteria for more than one ED within their lifetime. This has led some authors to proposes an alternative 'transdiagnostic' approach to ED (Fairburn & Bohn, 2005). Essentially this approach proposes creating a single unitary diagnoses of 'eating disorders', which encompasses AN, BN and EDNOS. The main argument for this approach is that several more similar characteristics are seen between the separate ED classifications than differential features (Fairburn & Bohn, 2005).

Prevalence and epidemiology of eating disorders

The reported prevalence of ED in the adult population vary between studies from 0.5%-1.0% for AN and 0.5-3.0% for BN. In a recent large representative sample (Swanson, Crow, Le Grange, Swendsen, & Merikangas, 2011) from the US, lifetime prevalence estimates of AN, BN and BED in an adolescent sample were 0.3%, 0.9% and 1.6%, respectively. However, prevalence of ED may be underestimated in the previous study since the sample consisted of adolescents only. Reports from a previous Finnish birth cohort estimate the lifetime prevalence of AN and BN to be 2.2% and 2.3% (Keski-Rahkonen, et al., 2009; Keski-Rahkonen, et al., 2007), respectively.

ED are more common in females than males, and it is reported in the DSM that the ratio of ED in males to females is 9:1 (American Psychiatric Association, 2000). The mean age of onset of an ED in an adolescent sample was recently reported to occur between the age of 12.3 and 12.6 years (Swanson, et al., 2011), significantly younger than previous investigations. In samples with a wider age-range, the typical age of onset for ED has been reported to occur between 15 and 16 years (Striegel-Moore, et al., 2005).

Prior to reviewing the specific literature on ED and motherhood, the following section provides a general overview of the topic of parental psychiatric disorders.

1.2.2 Parental psychiatric disorders

Psychiatric disorders can commonly occur during pregnancy and in the post-natal period. It is estimated by the Royal College of Psychiatrist that between 30% and 60% of those with a severe psychiatric illness have children (Bailey & Shooter, 2010). Psychiatric illness can have detrimental effects on pregnancy, as well as interfere with general parenting function. The implications of a parental mental illness are therefore not limited to the parent and can have long-term consequences for their child's cognitive and emotional development (Rutter & Quinton, 1984).

It is well documented that children of parents with a mental illness have an increased risk of developing psychological disturbances and psychiatric disorders themselves (Rutter & Brown, 1966; Rutter & Quinton, 1984). The exact mechanisms for the associations between parental psychiatric illness and psychological problems in their children are currently unknown, but are likely to involve a combination of psychological, social and genetic factors (Goodman & Gotlib, 1999). However, not all

children whose parents have a psychiatric illness go on to develop problems themselves and protective factors, such as strong social networks, may increase the resilience of a child to particular risk factors.

Within the study of ED the topic of pregnancy and motherhood, and the implication for their children, has only been investigated more recently. Nevertheless, there is evidence that ED can affect parenting ability and have adverse outcomes for their child's development (Patel, Wheatcroft, Park, & Stein, 2002). Furthermore, children of mothers with an ED have an increased risk of developing disordered eating themselves, and as such it has been proposed that a cycle of risk may be occurring, perpetuating ED across generations (Bulik, Reba, Siega Riz, & Reichborn Kjennerud, 2005). Gaining a greater understanding of the associations between ED, pregnancy and child development may extend our current understanding of the risk of intergenerational transmission of ED.

1.3 Methodological considerations

There are several general methodological issues relating to the following literature that should be considered when interpreting the findings presented within this chapter. Specific methodological issues pertaining to individual studies will be discussed throughout this literature review.

Earlier studies of women with ED and their children have tended to rely on small clinical samples, which are limited by their design. The participants in these studies are often not representative of general populations, since they have been recruited from specialist services, such as: ED inpatients and outpatients, perinatal services and fertility clinics. The design of these studies is further limited since they frequently lack a control group and fail to use standardised research assessments. More recently, several larger longitudinal studies are providing new evidence within this field of research; most notably from cohorts such as the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Norwegian Mother and Child cohort study (MoBa).

1.4 Pre-conception and fertility

The typical age of onset of ED has typically been reported as occurring during early adolescence. Developing an ED at such a critical time of female reproductive development can result in delays to adolescent sexual development and in menstrual

and ovulation problems. In general, fertility is thought to be decreased in women with ED; however, the association between fertility and ED is currently not well-established.

1.4.1 Menstrual and ovulation dysfunction

Amenorrhea has been characteristic of AN since the first descriptions of the illness (e.g. Gull, 1874), and it is currently a clinically diagnostic feature. A return to normal weight appears to be an important factor in regaining normal menstruation in women with AN, and many studies have reported normal fertility in women with AN who have achieved a healthy weight. Golden et al (1997) reported that 86% of females with AN resumed menses within six months of regaining weight. Furthermore, women resumption of menses has been found to fluctuate according to the season; and the probability of resumption of menses in AN has been found to be two-fold during warm seasons (Favaro and Santonastaso, 2009). Women with ED may therefore have improved fertility in spring/summer seasons compared to autumn/winter. However, it is likely that the prevalence of amenorrhea remains higher in those who have recovered from AN than in the general population (Kohmura, Miyake, Aono, & Tanizawa, 1986) and it has been reported to persist in up to 30% of women who have recovered from an ED (Falk & Halmi, 1982).

However, amenorrhea is not always present in women who would otherwise meet criteria for AN, and is often difficult to assess when patients are taking hormonal contraception (Abraham, Pettigrew, Boyd, Russell, & Taylor, 2005). Therefore, amongst other factors, the usefulness of amenorrhea to diagnose AN has been highly debated, prompting the proposal that this criteria be removed in the upcoming fifth edition of the DSM (Attia & Roberto, 2009).

Although less is known about menstruation problems in women diagnosed with BN and EDNOS, disturbed menses are also apparent. Despite maintenance of a normal weight being more common in women with BN and EDNOS, amenorrhea or oligomenorrhea are often reported (Crow, Thuras, Keel, & Mitchell, 2002; Morgan, 1999b; Pirke, et al., 1987; Schweiger, Pirke, Laessle, & Fichter, 1992). Menstrual dysfunction has also been highlighted in females with subclinical ED or women who regularly diet (Bates, Bates, & Whitworth, 1982; Kohmura, et al., 1986; Kreipe, Strauss, Hodgman, & Ryan, 1989). This emphasises that disruption to the menstrual cycle is unlikely to be related to body

weight alone. Remaining ED related behaviours and attitudes in those with a history of an ED or with sub-threshold disorders, may also have a negative impact on hormonal balance and fertility, despite normal weight gain (Falk & Halmi, 1982).

1.4.2 Conception and fertility problems

Given the disruption to menstrual patterns highlighted above, women with ED may experience difficulties conceiving. Despite this, very few studies have attempted to determine the association between fertility and ED, amongst those that have, there have been conflicting results.

Only two small studies have examined the prevalence of ED in women with infertility, both found similarly high levels. In the first study, 66 infertile patients were screened for an ED; 7.6% of women met criteria for lifetime AN or BN, this figure increased to 16.7% when EDNOS was additionally accounted for (Stewart, Robinson, Goldbloom, & Wright, 1990). Furthermore, a higher proportion of women (58%) met criteria for an ED diagnosis when women were assessed for more general menstrual problems.

More recently, Freizinger and colleagues (2008) found that 20.7% of women starting their first gonadotropin/intrauterine insemination (IUI) treatment cycle in a fertility clinic, met criteria for past or current AN or BN. In this particular study, at the time of screening no participants were underweight and there was no difference in the BMI of women with a history of ED or women without an ED. Additionally, a high proportion (8.5%) of women with past or current BED receiving fertility treatment was reported. Although BED has not received a great deal of attention in the fertility literature, Sbaragli et al (Sbaragli, et al., 2008) also found the prevalence of BED was more common in infertile females than in female controls.

The relationship between infertility and ED has also been investigated by studying the frequency and prevalence of pregnancies in this group. In a long-term follow-up study of women previously hospitalised for AN, the number of women who gave birth was found to be reduced to one third of that expected (Brinch, Isager, & Tolstrup, 1988). In contrast, other studies have found the frequency of pregnancies or fertility treatment in women with ED to be comparable to the general population in women with both AN (Bulik, et al., 1999) and BN (Crow, et al., 2002). The contrasting findings across these studies may suggest that psychosocial factors such as not having a partner or choosing

not to have children may be contributing to the reduced number of births in women with AN. Alternatively, methodological issues such as differing lengths of follow up as well as the severity of the ED and age of the study population may also contribute to the differences in findings, and further research is required.

Only one study has investigated differences in time taken to conceive in women with BN, which is a more sensitive measure of fertility problems, and concluded that fertility was not significantly affected in this group (Crow, et al., 2002). There is a strong need for replication of these findings in larger samples and investigation of other ED.

The frequency of unplanned pregnancies appear to be more common in women with BN (Morgan, Lacey, & Chung, 2006), and recent findings also indicate that they may be higher in women with AN (Bulik, et al., 2010). Although the reasons for elevated levels of unplanned pregnancies in women with ED remain unknown, it has been suggested that women experiencing irregular or apparently absent menstrual cycles may mistakenly believe that they have reduced fertility (Morgan, et al., 1999c).

1.4.3 Sexual development and relationships

Menstrual and ovulation dysfunction is only one possible factor for potentially reduced fertility in this group and psychosocial factors such as desire for a child, marital status and sexual development are also likely to be important (Maxwell, et al., 2010). Although it has been reported that the desire for an intimate relationship is not reduced in women with ED (Schmidt, Evans, Tiller, & Treasure, 1995), unstable relationship and lower levels of intimacy appear to be more common (Pinheiro, et al., 2010; Van den Broucke, Vandereycken, & Vertommen, 1995a, 1995b) and may contribute to reduced pregnancies in this group.

Differential patterns of sexual behaviour and attitudes have also been observed in women with ED (Pinheiro, et al., 2010; Schmidt, et al., 1995), but appear to be most pronounced in those with AN. Not only are attitudes towards sexuality more negative in females with AN (Ruuska, Kaltiala-Heino, Koivisto, & Rantanen, 2003) but delays in sexual behaviour, such as the first sexual experience, are also more common (Ruuska, et al., 2003; Schmidt, et al., 1995) than in both bulimic and healthy control groups. Attitudes towards sexuality tend to be more positive in females with BN (Ruuska, et al., 2003) than those with AN. Females with BN report being more sexually experimental

and experienced, considering themselves to have a higher than average libido (Abraham, et al., 1985), although such attitudes appear to vary according to their current weight (Abraham, 1998; Morgan, 1999b).

This overview of the literature indicates impairment of menstrual and ovulation in women with ED, coupled with differential patterns of sexual development and difficulties with relationships, therefore compromised fertility may be expected. However, investigations of fertility in women with ED continue to show conflicting results.

1.5 Eating disorders and pregnancy

The endocrine abnormalities, sexual and relationship problems associated with ED (section 1.4) has meant that for a long time pregnancy was thought to be unusual in this group of women. However, oligomenorrhea and amenorrhea do not necessarily indicate anovulation, and gestation may begin without prior menstruation (James, 2001; Mitchell-Gieleghem, Mittelstaedt, & Bulik, 2002), or at a severely low body weight (Manzato, Zanetti, & Gualandi, 2009). There are several cases cited in the literature of women suffering with severe and protracted AN becoming pregnant (Manzato, et al., 2009; Mazer-Poline & Fornari, 2008; Namir, Melman, & Yager, 1986; Rand, Willis, & Kuldau, 1987).

The number of women with ED becoming pregnant is currently unknown since few studies have investigated the prevalence of pregnancy in women with ED. Bansil (2008) reported that the number of women with an ED delivering babies in the United States (US) was 0.39 per 10,000 deliveries. However, this study only investigated live births and may not accurately reflect the number of pregnancies in this group of women. Results from the MoBa cohort study estimated that the pre-pregnancy prevalence of ED was: 0.1, 0.7 and 3.5, for AN, BN and BED respectively (Bulik, et al., 2007). However, the prevalence of ED during pregnancy may be underestimated since women often do not disclose their illness with healthcare providers when seeking fertility treatment or during pregnancy (Freizinger, et al., 2008; Morgan, et al., 2006). This highlights the need for healthcare providers to adequately screen for ED during pregnancy and in women who are experiencing difficulties conceiving.

1.5.1 Pregnancy outcomes in women with eating disorders

ED during pregnancy are associated with difficulties carrying a child to term, and the risk of miscarriage and terminations of pregnancy are reportedly elevated in women with ED. Strikingly, an early retrospective follow-up of 140 women previously hospitalised for AN found the rate of perinatal lethality to be six times the expected (Brinch, et al., 1988). Although nine women within in this sample had active AN throughout pregnancy, a large proportion (72%) had recovered from the disorder when they delivered their babies. However, this study was retrospective in nature, and therefore maybe subject to recall bias, particularly with reference to the course of ED symptoms.

In women with AN, the prevalence of miscarriages are also elevated (Bulik, et al., 1999; Ekeus, Lindberg, Lindblad, & Hjern, 2006). A study by Bulik and colleagues (1999) found that miscarriages were more than twice as high in women with AN (38% vs 16%), compared to a healthy control group. In this study there was also a strong trend for women with AN to have more elective terminations of pregnancy compared to controls.

There is also evidence for an increased risk of miscarriage in women with BN, particularly when women are in an active phase of the illness at the time of conception (Abraham, 1998; Mitchell, Seim, Glotter, Soll, & Pyle, 1991). Morgan and colleagues reported a 2.6 increase in risk of miscarriage in women with active BN compared to women with remitted BN (Morgan, et al., 2006). These findings to a large extent been confirmed in recent epidemiological studies; Micali and colleagues (Micali, Simonoff, & Treasure, 2007) found higher miscarriages in women with lifetime BN, but not in those reporting AN alone.

Several other pregnancy complications have been associated with ED, such as: gestational diabetes (Micali, Simonoff, et al., 2007a) preeclampsia (Ekeus, et al., 2006; Madsen, Hørder, & Støving, 2009) and hyperemesis gravidarum (Torgersen, et al., 2008), but have not been confirmed in others (Bansil, et al., 2008). Pregnancy complications such as these have been researched to a lesser degree and the distinction between ED subtypes remains unclear.

1.5.2 Psychopathology during pregnancy

Given the changes to weight and shape throughout gestation, it could be expected that pregnancy can be particularly difficult time for women with ED. As such, some studies have reported that pregnancy can exacerbate ED symptoms (Conrad, Schablewski, Schilling, & Liedtke, 2003) or be a trigger for the development of an ED (Tiller & Treasure, 1998). However, the majority of studies have reported that ED attitudes and behaviours tend to reduce during pregnancy in women previously diagnosed with an ED (Blais, et al., 2000; Bonne, Rubinoff, & Berry, 1996; Crow, Agras, Crosby, Halmi, & Mitchell, 2008; Lacey & Smith, 1987; Micali, Treasure, & Simonoff, 2007b; Morgan, Lacey, & Sedgwick, 1999c). Bulik and colleagues (Bulik, et al., 2007) reported that the proportion of ED remitting during pregnancy ranged from 29-78%, dependent on ED classification. Whilst reductions in ED behaviours, such as binge eating and self-induced vomiting (SIV), have frequently been reported, high levels of weight and shape concerns may be more likely to persist during pregnancy (Micali, Treasure, et al., 2007b).

Given these findings, it has been suggested that for many women pregnancy may represent a motivational time for women with ED to discontinue behaviours that may be harmful to their unborn child, and an optimal time for psychological intervention (Micali, 2010).

Reduced ED attitudes and behaviours during pregnancy have been more commonly found in women with BN rather than AN (Blais, et al., 2000). Few studies have investigated the course of symptoms during pregnancy in women with EDNOS; nevertheless, it has been indicated that continuation of symptoms during pregnancy may be more common than remittance in women with BED (Bulik, et al., 2007). Furthermore, reported reductions in ED symptoms during pregnancy do not represent a complete recovery and symptoms typically resurge within the first six to twelve months post-partum (Astrachan-Fletcher, Veldhuis, Lively, Fowler, & Marcks, 2008; Micali, Treasure, et al., 2007b). These findings highlight the need for consistent care for women with ED both during pregnancy and in the post-partum period.

Co-morbid psychiatric illnesses are common in women experiencing an ED, particularly levels of depression and anxiety (Hudson, Hiripi, Pope, & Kessler, 2007). Despite this,

few studies have investigated levels of co-morbid psychopathology during pregnancy in women with ED. An early study indicated that women with ED displayed more pregnancy related anxieties, specifically for the well-being of their unborn child and weight gain during pregnancy (Lemberg & Phillips, 1989). Furthermore, Carter and colleagues (2003) found that 40% of women with ED had a major depressive episode during the year of childbirth. Similarly, in a twin based study, women with ED were also found to commonly experience depression during pregnancy; 39% and 59% of women with AN and BN respectively (Mazzeo, et al., 2006).

These findings have recently been confirmed in a large epidemiological study utilising data from the ALSPAC cohort; Micali and colleagues (2010) reported that women with a history of ED had an increased risk of high levels of anxiety and depression during pregnancy. Women who continued to experience high levels of ED symptoms during pregnancy and had a past history of depression were at the greatest risk of experiencing depression and anxiety during pregnancy. This scarce research indicates that co-morbid psychiatric illness is common in women with ED during pregnancy. However, the relationship with obstetric and child outcomes has not been investigated.

1.5.3 Birth outcomes

The existing literature on birth outcomes is increasingly indicative of a relationship between maternal ED and adverse birth outcomes. The most well documented findings from studies of birth outcomes in women with ED, particularly those with AN are: premature delivery, low birth weight and reduced head circumference and intrauterine growth restriction in their offspring (Abraham, 1998; Brinch, et al., 1988; Bulik, et al., 1999; Conti, Abraham, & Taylor, 1998; Ekeus, Lindberg, Lindblad, & Hjern, 2006; Koubaa, Hallstrom, Lindholm, & Hirschberg, 2005; Mazor, et al., 1994; Micali, Simonoff, et al., 2007a; Morgan, et al., 2006; Sollid, Wisborg, Hjort, & Secher, 2004; Stewart, Raskin, Garfinkel, MacDonald, & Robinson, 1987).

Several studies have reported that women with ED are at risk of delivering lower birth weight babies (Bulik, et al., 1999; Sollid, et al., 2004; Stewart, et al., 1987). Koubaa and colleagues reported significantly lower birth weights in 49 women with a past or current ED diagnosis, women with AN in particular were found to have an elevated risk of low birth weight deliveries (Koubaa, et al., 2005). More recently, larger epidemiological

samples have found conflicting results. Whilst women with AN were found to have an elevated risk of lower birth weights in the ALSPAC study (Micali, Simonoff, et al., 2007a), results from the MoBa failed to confirm this finding (Bulik, et al., 2009). Predictors of neo-natal low birth weight in these studies included: smoking, low maternal pre-pregnancy weight and low weekly weight gain. In comparison to the low birth weights often observed in women with AN, significantly elevated birth weights, and a higher risk for delivering babies that were large for gestational age, have been reported in women with BED (Bulik, et al., 2009).

Previous studies in clinical samples of women with ED have also indicated an increased risk of premature delivery and preterm birth (Bulik, et al., 1999; Sollid, et al., 2004). In the study by Bulik and colleagues, birth outcomes were found to differ according to AN sub-type, and those who restricted food intake had an increased rate of delivering babies with a low gestational weight, compared to those who purged.

However, these studies are subject to some methodological limitations, such as relying on retrospective report and including only women who had received treatment for an ED. Larger longitudinal studies have failed to confirm previous findings of premature deliveries in women with ED (Franko, et al., 2001; Micali, Simonoff, et al., 2007a). In contrast to previous reports, findings from the MoBa cohort indicated that women with AN and BN had a lower risk of premature deliveries; conversely this was elevated in women with EDNOS (purging type) and BED (Bulik, et al., 2009).

Maternal ED during pregnancy may adversely impact on foetal growth and development. For example, in a case series of women receiving treatment for AN, diminished intrauterine growth was observed in five of the seven pregnancies, whereby the abdominal circumference of all babies was found to be significantly lower than average at birth (Treasure & Russell, 1988). Furthermore, a higher risk of reduced head circumference at birth has also been observed in the offspring of women with ED (Koubaa, et al., 2005). Koubaa and colleagues reported that the frequency of microcephaly was significantly elevated in offspring of women with ED; 8% compared to 2.5% in the general population.

This overview of the literature suggests that in general ED symptoms tend to improve during pregnancy. On the other hand there is accumulating evidence of an association between maternal ED and adverse pregnancy and birth outcomes.

1.6 *In utero* risk mechanisms for adverse perinatal outcomes

The potential risk mechanisms for adverse obstetric outcomes in ED have not been well studied, and to date there is no systematic research investigating the role of mediating and moderating factors for adverse pregnancy and birth outcomes in women with ED. Obstetric complications have been identified as a risk factor for childhood health and development, as well as playing a potential role in the intergenerational transmission of ED (Bulik, et al., 2005). The following section explores the current literature and possible risk factors for adverse obstetric outcomes in women with ED.

Substantial literature indicates that the *in utero* environment can affect both short-term (foetal and infant) and long-term (child and adulthood) development. However the underlying mechanisms are complex and not yet fully understood. In women with ED, two predominant pathways have been proposed (Micali & Treasure, 2009), resulting from environmental alterations during pregnancy: inadequate nutrition and elevated stress during pregnancy. These mechanisms are not mutually exclusive and the underlying physiological pathways overlap. The hypothalamic pituitary adrenal (HPA) axis is thought to play a crucial role. Given the risk of elevated stress and inadequate nutrition to women with ED, investigating both pathways during pregnancy is of clear importance.

1.6.1 Foetal programming

Foetal programming describes the process whereby the *in utero* environment during pregnancy influences the development of the foetus, and consequently the offspring's development throughout life, ascertaining that life in the womb programs health and development across the lifespan (Godfrey & Barker, 2001). Also known as 'the Barker hypothesis' because of the original work of Barker (Barker, 1990) who reported that intrauterine under-nutrition can lead to permanent changes in body structure and metabolism, leading to increased risk of metabolic disease later in life. In the last decade this has become an area of increasing research, and there is now strong evidence support the Barker hypothesis (Barker, 1998; Cottrell & Seckl, 2009).

1.6.2 Stress in pregnancy

There is a growing body of literature indicating that maternal mood during pregnancy can affect the intrauterine environment, increasing the risk of obstetric complications and have enduring effects on the psychological development of the offspring. High levels of stress, anxiety and depression are not unusual in pregnancy, and as highlighted above (section 1.5.2) may be particularly high in women with ED.

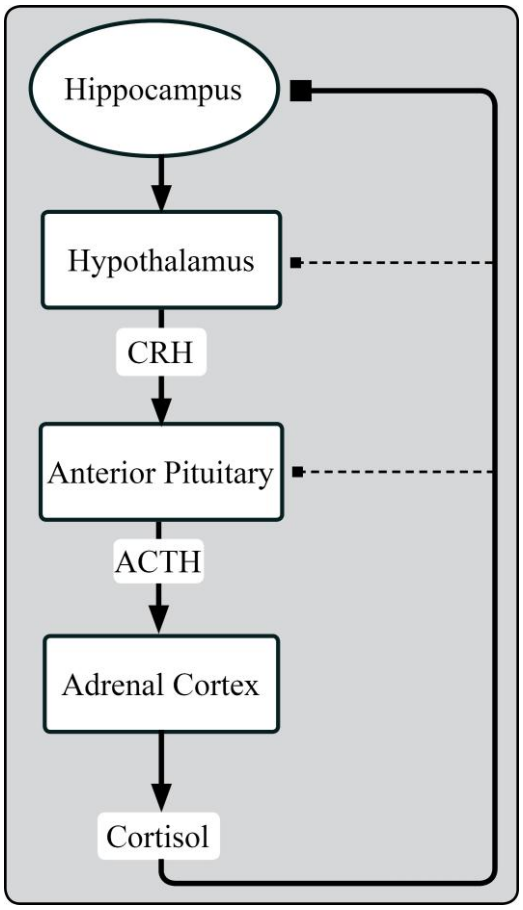
Stress is a multidimensional term, referring to both complex psychological and physiological processes. Within the literature pre-natal stress refers to 1. subjective stress (e.g. feelings of stress and anxiety) and 2. physiological responses to stress (e.g. levels of cortisol).

The Hypothalamic Pituitary Adrenal axis

The Hypothalamic Pituitary Adrenal (HPA) axis (Figure 1.1) is one of the major biological systems involved in modulating stress, and is thought to play an important role in foetal programming (Meaney, Szyf, & Seckl, 2007; Sandman, Davis, Buss, & Glynn, 2011).

Under normal circumstances the HPA axis has a diurnal pattern, characterised by high levels of stress hormones in the morning, which reach a nadir in the evening. The HPA axis is programmed to respond rapidly to stressful situation and return to homeostasis once the threat has passed. When the body perceives stress, cells in the hypothalamus are stimulated to produce corticotrophin-releasing hormone (CRH). This, in turn, stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary into the bloodstream, which is detected by receptors on the cortex of the adrenal gland; resulting in the release of glucocorticoids (steroid hormones) from the adrenal. Glucocorticoids (of which cortisol is thought to be the most important in humans) bind to glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) and immediately interact with these receptors to inhibit the stress response to return the body to homeostasis (Figure 1.1). However, under situations of chronic stress the HPA axis alters and can result in either prolonged elevations or reductions in cortisol, consequentially it is unable to respond appropriately to stressful situations (Gunnar & Quevedo, 2007; Johnson, Kamilaris, Chrousos, & Gold, 1992).

Figure 1.1: Stress and the HPA axis



During pregnancy the maternal HPA axis dramatically alters: first, there is a substantial increase of stress hormones across gestation (Sandman, et al., 2011) and second, the maternal stress response is dampened (Kammerer, Adams, von Castelberg, & Glover, 2002; Schulte, Weisner, & Allolio, 1990). In pregnancy cortisol stimulates the expression of hCRHmRNA in the placenta, resulting in a positive feedback loop which allows an increase of CRH to be released from the placenta (Sandman, et al., 2011). Although these stress hormones are necessary for foetal maturation, if excessive levels reach foetal circulation they can have adverse effects on development (Ginty, Phillips, Higgs, Heaney, & Carroll, 2011).

The placenta plays a key role in modulating the relationship between maternal and foetal stress hormones (O'Donnell, O'Connor, & Glover, 2009). While maternal levels of cortisol increase in pregnancy, foetal exposure is regulated by a placental enzyme 11β-hydroxysteroid dehydrogenase (11 β-HSD2), which inactivates glucocorticoids into

inactive 11-keto metabolites, acting as a barrier of glucocorticoid transfer from mother-to-foetus (Benediktsson, Calder, Edwards, & Seckl, 1997).

Psychiatric illness appears to shape the physiology of the stress system and different psychopathology is associated with different physiological profiles. For example, whilst levels of cortisol have been shown to be elevated in people suffering from depression and generalised anxiety disorder, low cortisol levels are associated with PTSD.

ED have also been associated with abnormalities of the HPA axis (Favaro, Monteleone, Santonastaso, & Maj, 2008). For example, plasma cortisol and CRH levels have both been shown to be elevated in women with AN (Boyar, et al., 1977; Hotta, et al., 1986; Kaye, et al., 1987), particularly in active phases of the illness. Some studies have indicated HPA axis functioning has been found to normalise in patients with AN after weight restoration (Brambilla & Monteleone, 2003).

Findings from investigations of HPA axis functioning in patients with BN are less conclusive. In general, circadian cortisol profiles in BN have been found to be either normal (Fichter, Pirke, Pöllinger, Wolfram, & Brunner, 1990) or elevated (Monteleone, et al., 2001). However, a recent investigation reported decreased diurnal salivary cortisol in participants whose BN was in remission (Birketvedt, et al., 2006).

Further evidence of HPA axis dysfunction in ED comes from studies measuring changes in salivary cortisol. For example, high levels of ED attitudes and behaviours (such as restraint, hunger, binge eating and body esteem) have been shown to be negatively related to the cortisol awakening response (Therrien, et al., 2008), indicating a blunting of HPA axis reactivity.

The effects of stress on obstetric outcomes

Heightened ante-natal maternal stress has been associated with an increased risk of negative pregnancy and birth outcomes, as well as more long-term emotional, behavioural and health problems in their children (see section 1.10). Studies from the animal literature have consistently found adverse obstetric outcomes, such as low birth weight and premature deliveries, utilising paradigms which induce stress during pregnancy (Mairesse, et al., 2007). Studies with humans do not allow for the same level

of experimental manipulation, nevertheless, in the last decade there has been increasing support for similar associations in humans.

A growing number of studies have indicated that women who experienced a disaster during pregnancy (such as: terrorist attacks, environmental/chemical disasters and natural disasters) have an increased risk of poorer birth outcomes (Harville, Xiong, & Buekens, 2011). For example, pregnant women who were in the World Trade Centre, or in close proximity, on the terrorist attracts of 9/11 (2001) delivered babies with significantly lower birth weights and lengths (Lederman, et al., 2004) and had a two-fold increased risk of intrauterine growth restriction (Berkowitz, et al., 2003). The strongest evidence emerging from studies of pre-natal exposure to disasters is for reduced foetal growth, by comparison gestational age appears relatively unaffected (Harville, et al., 2011).

It is not just stress arising from extreme disaster that is associated with adverse obstetric outcomes, several studies have indicated that milder stressors in the pre-natal period such as job strain (Oths, Dunn, & Palmer, 2001), stressful life events (e.g. divorce, moving house) and appraisal of stressful situations (Hedegaard, Henriksen, Secher, Hatch, & Sabroe, 1996) may also increase the risk of adverse obstetric outcomes. In a large prospective study by Hedegarrd and colleagues (1993), a dose-response relationship between general distress and preterm delivery was reported at 30 weeks gestation. In this study no relationship between general distress at 16 week gestation and preterm delivery was found, suggesting that there may be critical periods during gestation where the effect of stress may be most harmful. Recently, pregnancy related anxiety has been shown to be a strong predictor of the length of gestation. In a study by Kramer et al (2009) extensive measures of stress and anxiety were completed by women in mid-pregnancy, only pregnancy related anxiety however was found to predict preterm birth. In this study women with high pregnancy anxiety had a 1.5 increase risk of early delivery.

The underlying mechanisms mediating the relationship between pre-natal stress and adverse outcome remain unknown, and much of our understanding comes from animal models. Nevertheless two predominant pathways have been proposed (Mulder, et al., 2002; Wadhwa, 2005; Wadhwa, Sandman, & Garite, 2001).

1. **Transplacental transport of maternal stress hormones** – as discussed in section 1.6.2 maternal stress can lead to increased levels of glucocorticoids and CRH. Glucocorticoids are necessary for foetal development and maturation of vital organs such as the heart, liver, lungs and kidneys. However, excessive levels of glucocorticoids in foetal circulation can be detrimental to foetal development (Sandman, et al., 2011). The placental enzyme 11 β-HSD2 is thought to protect the foetus from harmful levels of glucocorticoids; accordingly, levels of glucocorticoids in foetal blood have been found to be up to 13 times less than in maternal circulation (Gitau, Fisk, Teixeira, Cameron, & Glover, 2001).

   However, 11 β-HSD2 only acts as a partial barrier of the transmission of stress hormones to the foetus and it has been reported that 10-20% of maternal plasma cortisol crosses the placenta (Gitau, et al., 2001). Furthermore, there is evidence that high levels of stress as well as poor nutrition during pregnancy can reduce the effectiveness of 11 β-HSD2 (O'Donnell, et al., 2009), allowing harmful levels of glucocorticoid to cross the placenta. It is thought that stress signals detected by the foetus result in an increase in placental CRH, advancing gestation and resulting in preterm delivery (Sandman, et al., 2011).

2. **Reduction in intrauterine blood flow** – pre-natal stress may also reduce maternal blood flow through activation of the autonomic nervous system, and therefore vascular transportation of oxygen and nutrients to the foetus. It has been proposed that reductions in intrauterine blood flood may in turn contribute to foetal growth restriction. There is some support for this hypothesis from doppler blood flow studies, which have indicated an association between high ante-natal anxiety scores and higher resistance of the uterine artery (i.e. reduced blood flow) (Teixeira, Fisk, & Glover, 1999). Similarly, Sjostrom and colleagues (1997) found a higher resistance index in the umbilicus of the foetus among women with a high trait anxiety score.

Aside from psychobiological changes highlighted above, maternal stress may also lead to alterations in lifestyle choices such as smoking, alcohol consumption and poor diet, which may also have harmful effects on foetal development.

1.6.3 Gestational weight gain

Pre-pregnancy weight and gestational weight gain are also likely to have effects on the intrauterine environment, and therefore be an important factor in obstetric outcomes. Women who gain insufficient weight during pregnancy have an increased risk of delivering premature and low birth weight babies, who are prone to infant mortality and morbidity (Abrams, Altman, & Pickett, 2000; Neggers, Goldenberg, Tamura, Cliver, & Hoffman, 1997; Siega-Riz, et al., 2010). Additionally, low maternal weight prior to pregnancy has been associated with preterm delivery (Sebire, Jolly, Harris, Regan, & Robinson, 2001). A recent systematic review concluded that low gestational weight gain was moderately associated with a range of adverse obstetric outcomes similar to those observed in women ED, particularly AN, such as: low birth weight, small for-gestational age and preterm birth (Viswanathan, et al., 2008).

In women with ED, some studies (Siega-Riz, et al., 2010) but not others (Koubaa, et al., 2005) have reported adequate weight or more weight gain than comparison groups during pregnancy, which may be protective against adverse obstetric outcomes (Bulik, et al., 2009; Siega-Riz, et al., 2010; Stewart, et al., 1987) . Pre-pregnancy weight in women with AN has also been shown to be a strong predictor of low birth weight (Micali, Simonoff, et al., 2007a). Conversely, women with BN and BED may have an increased risk of excessive weight gain during pregnancy (Siega-Riz, et al., 2010), which has also been associated with increased pregnancy and birth complications (Viswanathan, et al., 2008). However, it is often difficult to assess the specific effect of maternal weight and weight gain on obstetric outcomes in women with ED in the literature described since data on maternal weight is frequently not presented or adequately controlled for.

Patterns of gestational weight gain rather than total weight gain during pregnancy may also be important for pregnancy and foetal outcomes. For example, a pre-pregnancy BMI below the normal range and inadequate weight gain in the third trimester has been found to nearly double the likelihood of delivering preterm infants (Siega-Riz, Adair, & Hobel, 1996). Similarly, Abrams and colleagues (2000) found that slow weight gain in the second and third trimester was associated with premature deliveries. However, deviant patterns of foetal growth may ultimately result in similar birth weights, highlighting the limitation of birth weight as a single measure of foetal development.

1.6.4 Nutritional intake during pregnancy

Pregnancy weight does not necessarily reflect adequate nutritional intake. Maternal nutrition is crucial for foetal growth and development, and nutritional intake both prior to conception and during pregnancy are related to birth outcomes (Fowles, 2004). Women with ED are likely to feel particularly unsure about sufficient nutritional requirements due to periods of dietary restriction and/or binging, which may become particularly distorted in pregnancy.

The topic of intrauterine nutrition has become of increasing interest to researchers, not least because of its recent links to chronic disease later in life (Barker, 1998, 2002). A number of epidemiological studies and animal experiments have highlighted the link between under-nutrition *in utero* and low birth weight and premature deliveries.

The relationship between specific nutrient intake and birth outcomes is unfortunately not well founded (Fowles, 2004), and it remains difficult to establish the independent role of nutrition on foetal development. Intake of various micronutrients is likely to have specific importance at different periods of gestation. For example, low birth weight, disproportionate head circumference and neonatal length are all indicative of lack of nutrients at particular stages of gestation (Barker & Clark, 1997). Additionally, low folate intake and iron deficiency during pregnancy have been linked to preterm deliveries and low neonatal birth weight (Allen, 1993, 2000; Scholl & Johnson, 2000).

Very few studies have specifically investigated nutritional intake during pregnancy in women with ED. However, there is preliminary evidence that nutrition during pregnancy differs in women with ED. In the ALSPAC cohort, women with AN had a higher intake of vegetables and less protein and fat consumption, compared to controls (Micali, Northstone, Emett, Naumann, & Treasure, in press). Additionally, Siega-Riz and colleagues (2008) found differing patterns of nutritional intake in women with BN and BED during pregnancy in the MoBa cohort. Specifically, women with BN and BED had higher intakes of fats and lower intakes of folate, potassium and vitamin C.

Poor ante-natal nutrition may also affect foetal development and birth outcomes via alteration of the HPA axis. As highlighted in section 1.6.2 the effectiveness of 11 β-HSD2 can be compromised by poor nutrition *in utero*. In rats a 50% reduction in protein

in their diets was found to decrease the activity of 11 β-HSD2 by 33%, and result in lower birth weight deliveries (Langley-Evans, et al., 1996).

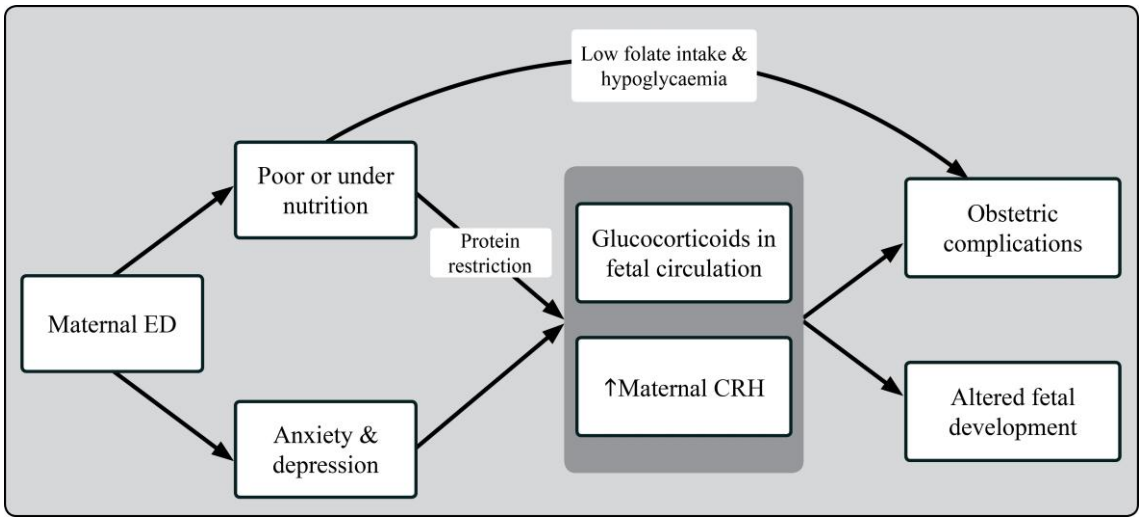
1.7 Hypothetical models of risk

Two theoretical models of risk have been proposed to describe: 1. how stress and nutrition during pregnancy might influence perinatal and infant outcomes in women with ED; and 2. how perinatal outcomes in women with ED may in turn increase the risk of developing an ED later in life. These two models are not mutually exclusive and provide some understanding of how maternal ED may lead to adverse perinatal and infant outcomes and consequently increase the risk of intergenerational transmission of ED.

1.7.1 Biological model of risk

The overview of the literature above highlights the possible mediating roles of nutrition and stress during pregnancy and obstetric and infant outcomes in women with ED. Micali and Treasure (2009) conceptualise this literature in a biological model of risk, which hypothesises the potential interaction of these factors via hyperactivity of the maternal and foetal HPA axis, see Figure 1.2. Two potential pathways are implicated in this model: poor nutrition (e.g. protein restriction) and co-morbid anxiety and depression in women with ED during pregnancy. These pathways are mediated by increased levels maternal CRH and consequentially elevated levels of glucocorticoids in the foetal circulation. It is hypothesised that elevated levels of glucocorticoids in foetal compartments in turn increases the risk of obstetric complications and alterations in foetal development in women with ED. Micali and Treasure highlight that under-nutrition during pregnancy may be particularly relevant to women with a history of AN, whereas alterations in glucose might be more relevant to BN.

Figure 1.2: Maternal eating disorders: a biological model of risk [3]



This model remains to be tested, and the *in utero* mediators of adverse outcomes in the offspring of women with ED are currently unknown. This literature highlights the need to investigate the potential pathways during pregnancy that may mediate both obstetric and infant outcomes in women with ED.

1.7.2 Perinatal cycle of risk

Not only do women with ED have an increased risk of perinatal complications, several researchers have theorised that perinatal complications might increase the risk of developing an ED later in life. It is beyond the scope of this thesis to investigate intergenerational transmission of ED, nevertheless it is interesting to consider the contribution of obstetric complications as a risk factor in the pathogenesis of ED.

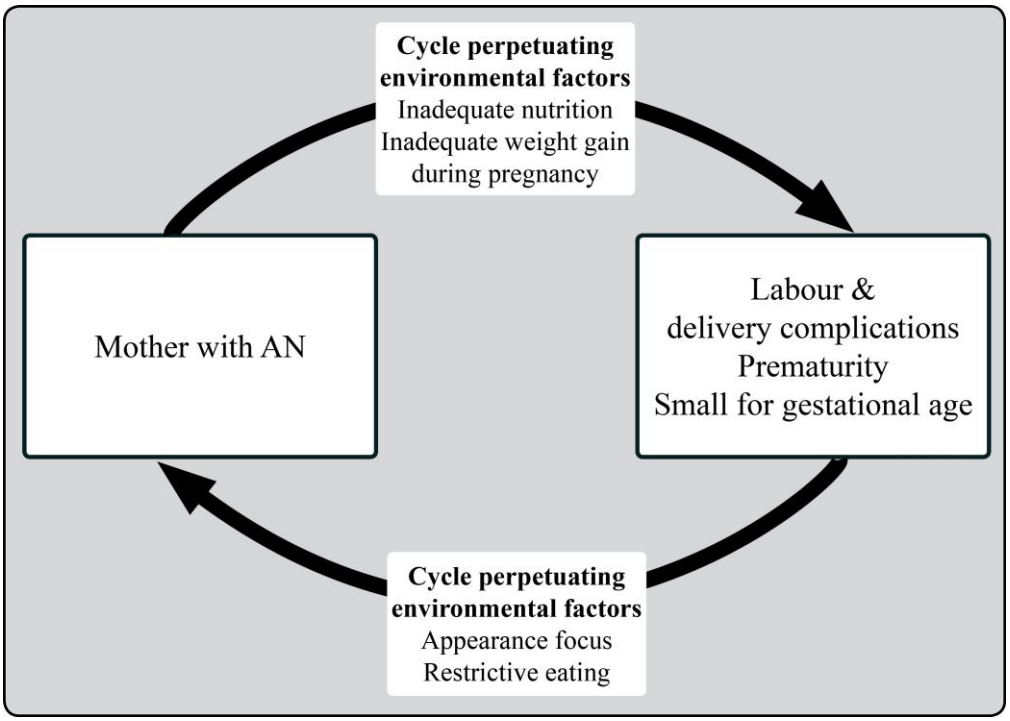
Evidence exists of an association between birth complications such as: prematurity, small for gestational age and cephalhematoma, and an increased risk of developing AN (Cnattingius, Hultman, Dahl, & Sparen, 1999; Favaro, Tenconi, & Santonastaso, 2006; Lindberg & Hjern, 2003). Such obstetric complications have also found been found to be proportionally and independently associated with an elevated risk of developing AN (Cnattingius, Hultman, Dahl, & Sparen, 1999), indicative of a causal relationship

[3] Figure adapted from Micali & Treasure, 2009

(Favaro, Tenconi, & Santonastaso, 2006). Clearly the aetiology of ED is complex and multidimensional, however it is indicated that perinatal risk factors may account for upto 3.6% of the risk of development of AN (Cnattingius, et al., 1999).

Bulik and colleagues (2005) propose that a cycle of risk may be occurring in women with AN, Figure 1.3, whereby AN increases the risk of labour and delivery complications which in turn increases the risk of developing AN. This cycle is thought to be perpetuated by poor intrauterine nutrition and post-natal environmental factors. Although researched to a lesser degree, perinatal complications have also been implicated in the pathogenesis of BN (Favaro, et al., 2006).

Figure 1.3: Cycle of risk in anorexia nervosa [4]



This theory is yet to be fully investigated and recent research has failed to support it (Bulik, et al., 2009; Wehkalampi, et al., 2010). It is possible that the cycle of risk may

[4] Figure adapted from Bulik, et al., 2005

only hold for very severe cases of AN (Lindberg & Hjern, 2003), or in the presence of other genetic or environmental factors. Therefore it is important to bear in mind that there are likely to be several interrelated factors implicated in the development of ED.

In summary, underlying mechanisms for obstetric complications in women with ED has not been adequately investigated. Pre-natal stress, gestational weight gain and poor nutrition during pregnancy are likely to contribute to poor foetal outcomes in this group; however this remains to be tested. Investigating these mechanisms in women with ED is an important area of research, since obstetric complications may represent a modifiable risk factor in the pathogenesis of ED.

1.8 The post-natal period

The post-partum period is not only a high-risk period for the recurrence of ED symptoms but is itself a trigger for the development of an ED (Bulik, et al., 2007; Stein & Fairburn, 1996). Although ED symptoms and behaviours tend to remit during pregnancy, findings indicate a recrudescence of symptoms after childbirth (Lemberg & Phillips, 1989; Morgan, et al., 1999c).

Mothers with ED have an increased risk of post-natal depression, which may affect up to one-third of women with BN (Abraham, Taylor, & Conti, 2001; Mazzeo, et al., 2006; Morgan, et al., 2006). Furthermore, elevated rates of depression and anxiety in women with ED in both pregnancy and in the post-partum period were identified in a large longitudinal prospective study in women with lifetime ED and active ED symptoms (Micali, et al., 2010).

1.9 Mothers with eating disorders: their infants and children

There is evidence that ED, like other psychiatric disorders, can interfere with general parenting abilities, which may impact on their child's development. ED behaviours such as binging and self-induced vomiting may directly interfere with mothering and catering to their child's needs (Fahy & Treasure, 1989; Lacey & Smith, 1987; Stein & Fairburn, 1989). Furthermore, more verbally controlling and intrusive parenting styles have been identified in women with ED, who tend to be less facilitating with their children (Stein, Woolley, Cooper, & Fairburn, 1994). Social factors such as unstable relationships and marital discord may also interfere with parenting function, and have implications for development in their offspring.

1.9.1 Maternal bonding and attachment

Very little is known about the early relationship between mother and baby in women with ED. A recent study found that more than 90% of women with a history of ED reported problems regarding their adjustment at three months post-partum, compared to 13% of controls (Koubaa, Hallstrom, & Hirschberg, 2008). In a review of the literature on ED in the post-natal period Astrachan-Fletcher and colleagues (2008) concluded that post-natal depression in mothers with ED, compounded with the body image concerns amplified by pregnancy, can negatively impact on mother and infant bonding and attachment in the post-partum period.

1.9.2 Childhood vulnerabilities

The offspring of women with ED also appear to be at an increased risk of certain vulnerabilities, in particular developmental, feeding and growth problems have been reported. In an observational study, Stein and colleagues found that children of mothers with ED were less happy and had lower emotional tone at 12 months compared to a control group (Stein, et al., 1994). Similarly, a prospective study of women with lifetime ED reported high levels of negative affect (e.g. sadness, crying and irritability) in their children (Agras, Hammer, & McNicholas, 1999). Although psychopathology is rare in young children, Brinch and colleagues (1988) reported that 2% of children whose mothers had ED were classified as "mentally ill", furthermore the mothers in this study reported that 7% of the children had "marked psychiatric problems".

1.10 Pre-natal stress and infant outcomes

Several prospective studies now indicate that pre-natal stress can have long-term implications for behavioural, emotional and cognitive outcomes in their offspring (Glover, O'Connor, & O'Donnell, 2009). Pre-natal stress or anxiety has been linked to lower scores on cognitive development (Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003) and language development (Laplante, Brunet, Schmitz, Ciampi, & King, 2008). The timing of stress also appears to be important; a study by Connor et al (2002) indicated that anxiety at 32 weeks gestation was more strongly associated with behavioural and emotional problems in the children than at 18 weeks gestation.

Furthermore, there is also good evidence that maternal stress or anxiety during pregnancy may have implications for future development of psychopathology such as

schizophrenia, autism and attention deficit hyperactivity disorder (ADHD) (Glover, et al., 2009).

1.10.1 Infant stress response

Maternal stress during pregnancy may also affect the infant's ability to respond appropriately to stressful situations. The relationship between maternal stress during pregnancy and stress reactivity in their infants is of increasing interest for several reasons. First, the way in which an infant or child responds to stressful situations is indicative of how they regulate their emotions and behaviour, and is crucial for healthy psychological development. Second, findings from the animal literature has indicated that altered functioning of the HPA axis in infancy may be linked to deficits in cognitive performance (Gué, et al., 2004), heightened emotionality (Weinstock, 1997) and behavioural problems (Griffin, Skinner, Salm, & Birkle, 2003).

As described in 1.6.2 the HPA axis is programmed to respond rapidly to stressful situations and return to homeostasis once the threat has passed. Alterations in infant stress reactivity appear to be in part determined by pre-natal maternal HPA axis activity; and thus a possible indication of a foetal programming effect (Huizink, Mulder, & Buitelaar, 2004; Yehuda & Bierer, 2007). In animal studies, there is strong evidence for a relationship between foetal exposure to high levels of glucocorticoids (endogenous and exogenous) and heightened physiological and behavioural stress reactivity in the offspring (Durand, Sarrieau, Aguerre, Mormede, & Chaouloff, 1998; Kapoor, Dunn, Kostaki, Andrews, & Matthews, 2006; Kapoor, Leen, & Matthews, 2008; Meaney, et al., 1994; Schneider, 1992). In humans, general anxiety during late pregnancy has been found to lead to higher basal cortisol concentrations in their children at 10 years (O'Connor, et al., 2005).

However, stress paradigms in humans, which measure infant reactions to stressors such as: painful stressors (e.g. heel prick and immunisations) or social stressors (e.g. strange situation and still face procedures) are only recently emerging (Davis, Glynn, Waffarn, & Sandman, 2011; Gutteling, de Weerth, & Buitelaar, 2004; Gutteling, Weerth, & Buitelaar, 2005; Tollenaar, Beijers, Jansen, Riksen-Walraven, & de Weerth, 2011).

In one of the most detailed studies to date, Davis and colleagues (2011) reported that high maternal cortisol levels in pregnancy were associated with a larger infant cortisol

reaction in new-borns to the heel prick test. Furthermore, higher levels of maternal perceived stress during pregnancy predicted a slower rate of recovery of behavioural stress responses. Similarly, Gutteling and colleagues (2004; 2005) found that elevated maternal cortisol and psychosocial stress measured at 15 to 17 weeks of gestation predicted higher cortisol levels on the day of an inoculation and on the first day of a new school year.

It is difficult to fully attribute such affects to the effect of stress *in utero* since maternal psychosocial measures of stress were often found to be unrelated to maternal cortisol measures in these studies (Davis, et al., 2011; Gutteling, et al., 2004; Gutteling, et al., 2005). Since the HPA axis continues to develop in the post-natal period, post-natal influences are also likely to be important. Post-natal effects have been found to play 'buffering' role in infants' reactions to stressful situations. For example, a recent study Albers et al (2008) found higher levels of care-giving in the post-natal period predicted better cortisol recovery from a mild stressor (i.e. a bathing routing). Nevertheless, maternal anxiety (in particular pregnancy specific anxieties and perceived stress) has been found to exert effects on infant stress reactivity, independent of post-natal factors (Tollenaar, Beijers, Jansen, Riksen-Walraven, & de Weerth, 2011).

Adversities other than stress and anxiety during pregnancy have also been associated with dysfunctional stress reactivity in infants and children such as: drug and alcohol exposure, childhood abuse, insecure attachments and family/environmental adversity and depression (Hunter, Minnis, & Wilson, 2011). Whilst most studies indicate that exposure to such adversities during pregnancy lead to increased cortisol reactivity some show a blunted response.

As discussed earlier infant stress regulation may be an early risk factor for developmental problems and psychopathology, recently, regulation of stress has also been implicated as a risk factor for the development of AN (Favaro, Tenconi, & Santonastaso, 2008, 2010). Favaro and colleagues found a combined effect of obstetric complications and childhood abuse on the risk of developing an ED later in life (Favaro, Tenconi, & Santonastaso, 2010). The authors previously reported that women with ED who were dysmature at birth were more likely to display a harm-avoidant temperament, and less able to cope with stressful situations (Favaro, Tenconi, et al., 2008). These

preliminarily findings suggest a potential role perinatal complications and pre-natal programming of the stress response in the pathogenesis ED.

1.11 Feeding and diet

Mothers with ED express concerns regarding their ability to provide an adequate diet for their children and increased anxiety around family mealtimes (Bryant-Waugh, Turner, Jones, & Gamble, 2007). Given the preoccupation with food and weight, characteristic of ED, catering for the nutritional needs of their children may be especially challenging for these mothers.

The family provides an important context for the development of dietary attitudes and behaviours (Birch & Fisher, 1998; Golan & Crow, 2004), accordingly, maternal diet has been shown to be one of the strongest predictors of childhood food consumption (Brion, et al., 2010). Children of mothers who have ED therefore represent a high risk group for developing abnormal dietary behaviours.

Case studies and small observational studies have indicated that children of mothers with ED have an increased risk of feeding difficulties in early childhood. Problematic breastfeeding, refusal of solids and more frequent use of food for non-nutritional purposes (e.g. as a means of reward) have been highlighted as potential areas of difficulty (Park, Senior, & Stein, 2003; Patel, et al., 2002). For example, in a case series of 11 women with AN and BN (Timimi & Robinson, 1996), it was found that nine of their children displayed disturbed patterns of eating in early childhood.

Larger epidemiological studies also provide evidence that mothers with ED experience difficulties feeding their infants. For example, mothers with ED of infants (birth to six months of age) in the ALSPAC were found to experience more feeding difficulties than the control group (Micali, Simonoff, & Treasure, 2009). Specifically, infants of women with AN were more likely to exhibit small quantity and slow feeding; whereas infants of women with BN more frequently refused solids.

In one of the only long-term follow up investigations of women with ED and their children, Stein and colleagues (Stein, et al., 1994) reported that mothers with an ED exerted more intrusive and controlling behaviours over their child's eating, and higher levels of conflict at mealtimes were observed when the children were 12-14 months old.

When followed up at ten years of age, the children of mothers with ED displayed more disturbed eating habits and attitudes, such as dietary restraint and overvalued ideas about weight and shape (Stein, Woolley, Cooper, et al., 2006).

Furthermore, mothers with ED also tend to hold more distorted perceptions of their child's weight and shape, which may have direct effects on their child's dietary intake, and in severe cases has been associated with reduction to their child's food intake and endorsement of dieting behaviour (Fahy & Treasure, 1989; Lacey & Smith, 1987; Timimi & Robinson, 1996; Waugh & Bulik, 1999). Furthermore, mothers with ED are also less likely to cook or engage in mealtimes with their children in order to limit the amount of time spent dealing with food (Woodside & Shekter Wolfson, 1990).

Despite evidence of an association between maternal eating pathology and a risk of feeding difficulties in their children, only one small case-control study (n=20) to date has investigated the quality of diet in children whose mothers have an ED (Waugh & Bulik, 1999). Although the authors reported no major differences in dietary intake compared to children in the control group, there was some indication that less junk food was being consumed by children of women with ED. However, this study was limited by small sample size, and a wide child age-range; further investigation utilising longitudinal data is required.

Despite the scarcity of large, comprehensive studies, there is some evidence that maternal ED affect child eating (Park, et al., 2003; Patel, et al., 2002). However, the majority of these studies lack a comparison group and have been restricted to feeding behaviours in early infancy. Robust studies of feeding and eating difficulties during middle childhood are rare, this is an important area of investigation since it represents an crucial time period for the development of dietary behaviours (Hill, Oliver, & Rogers, 1992). Furthermore, there are no large of longitudinal investigations of the quality of diet and patterns of eating in children of mothers with ED.

1.12 Growth

Given the evidence of an increased risk of feeding styles and potential different dietary behaviours in children of women with ED highlighted above, the growth children of mothers with ED is important area of concern, which remains under researched. Despite

a lack of research in this area there is preliminary evidence to suggest growth in children of mothers with ED may be adversely affected.

As highlighted earlier (1.5.1) maternal ED during pregnancy, particularly AN, are associated with an increased risk of intra-uterine growth restriction and small birth weight deliveries (Micali, Simonoff, et al., 2007a; Treasure & Russell, 1988). Whilst preliminary studies have suggested adequate post-natal catch up growth (Stein & Woolley, 1996; Waugh & Bulik, 1999), others indicate that poor growth may continue throughout infancy and childhood (Stein & Fairburn, 1989; Timimi & Robinson, 1996; van Wezel-Meijler & Wit, 1989). For example, in a study of eight mothers with AN it was found that their children were food deprived and had severely reduced weight and height for their age (Russell, Treasure, & Eisler, 1998). Furthermore, in a small study of 13 mothers with ED (Hodes, Timimi, & Robinson, 1997), 32% reported that their offspring had abnormal weight or growth for their age. Children of women with AN in this study, in particular female children, were found to be lighter than children of women with BN and there was evidence of wasting in 46% of the children investigated.

These findings have, to some extent, been confirmed in larger prospective and longitudinal studies of women with ED and their children. In a prospective study of 140 mothers with AN, 28% of mothers reported that their children had feeding and weight difficulties, and 17% reported 'failure to thrive' within their first year of life (Brinch, et al., 1988). However, feeding and growth in this particular study was obtained from maternal self-report, which may be subject to bias. Women with ED may have particular difficulty judging their children's food intake or weight; therefore objective measurements of feeding and growth are crucial within this group of women.

Similarly, Stein and colleagues (Stein, et al., 1994) found children of women with ED had lower weight gain at one year compared to controls, which was associated with higher levels of mealtime conflict (Stein, et al., 1994). When the children were followed up at ten years of age the BMI of the children born to mothers with ED were comparable to the control group (Stein, Woolley, Cooper, et al., 2006). These authors further reported that children of women with ED were smaller than children of women with post-natal depression, whose weight did not differ from the healthy control group (Stein, Murray, Cooper, & Fairburn, 1996). Suggesting that in this study infant growth in the first year of life was specific to eating pathology rather than more general

psychopathology, this finding requires replication and further investigation later in childhood.

The majority of the studies to date have focused on mothers with AN or BN separately, or fail to distinguish between ED classifications, however there is preliminarily evidence that infant growth patterns may differ according to ED classification. While studies of children of women with AN have highlight reduced growth in their offspring (Hodes, et al., 1997; Timimi & Robinson, 1996; van Wezel-Meijler & Wit, 1989); there is some evidence that maternal BN is associated with more rapid growth or obesity (Hodes, et al., 1997; Micali, et al., 2009; Stein & Fairburn, 1989). For example, previous findings from ALSPAC have indicated that maternal BN is associated with an increased risk of their children and being overweight at nine months, compared to a control group. In this particular study infant growth of the children of mothers with AN was similar to the control group (Micali, et al., 2009). However, the majority of previous investigations have been limited by small sample size and include children at different ages, making the findings difficult to generalise.

Some studies, which have investigated the role of child gender on growth, have indicated that mothers with ED show greater concern for their daughter's weight and shape than sons (Agras, et al., 1999). Female children of mothers with ED may therefore have a higher risk of altered growth patterns than male children. Only one small case study has reported that girls of women with ED were more likely to be underweight than boys (Hodes, et al., 1997). However, the sample size in this study was small, and further investigation of the influence of gender on childhood growth is required.

The majority of studies investigating growth in children of women with ED are cross sectional or confined to studying growth in early infancy. Therefore, it remains unclear whether adverse growth patterns identified it children of mothers with ED persistent throughout childhood. Furthermore, many of the studies discussed are subject to limitations, often relying upon small sample size consisting of patients with severe ED, and do not differentiate between ED classifications.

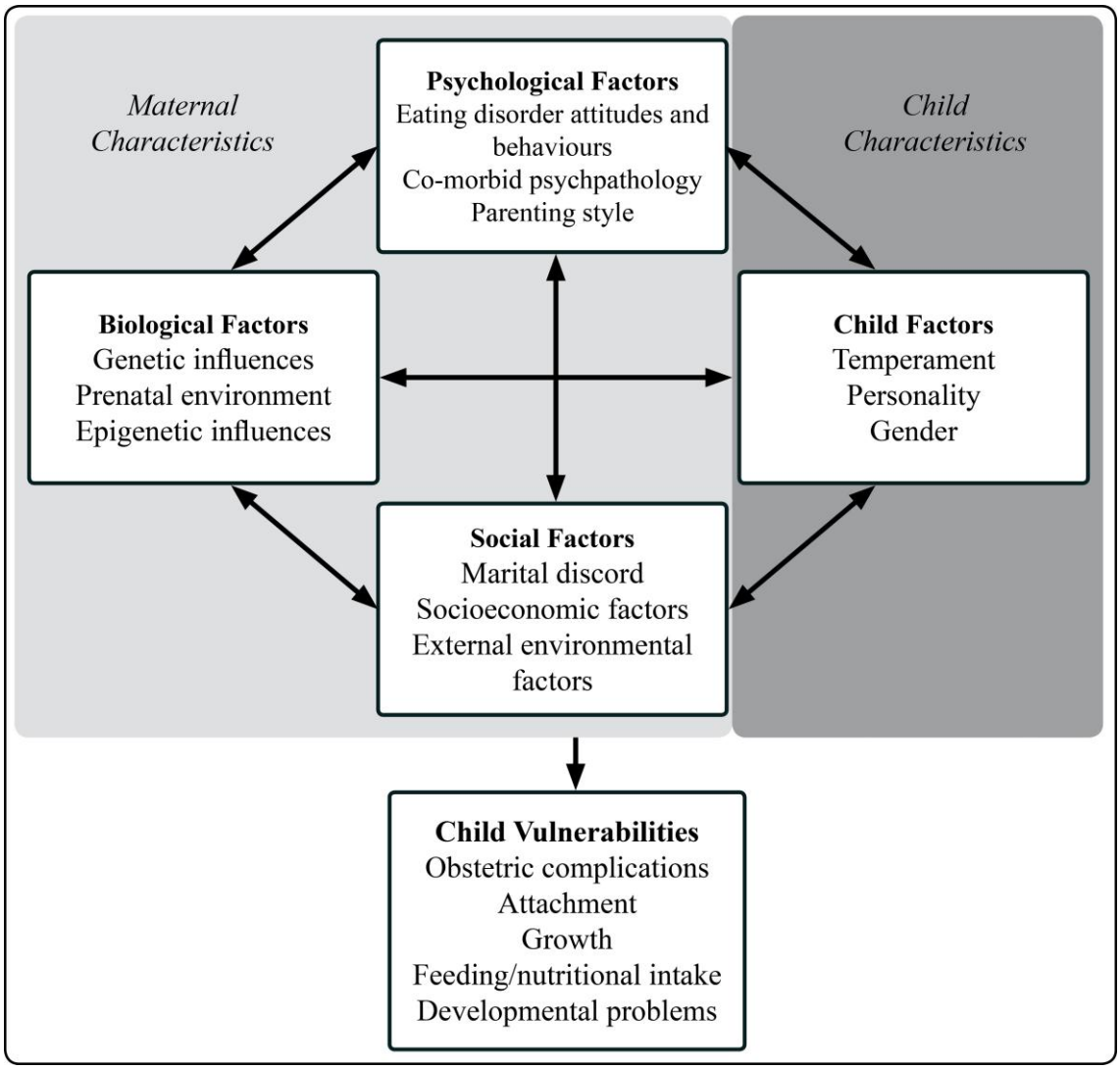
1.13 Conclusion

In conclusion, the pre-conception period, pregnancy and post-natal period pose challenges for women with ED. Psychobiological and social factors, associated with a maternal ED, may predispose their infants and children to certain vulnerabilities, such as: difficulties with stress regulation, diet and growth.

The underlying processes involved are likely to be complicated; nevertheless researchers have proposed several underlying factors in the relationship between maternal ED and the risk of adverse outcomes in their offspring (Park, et al., 2003; Patel, et al., 2002).

In order to conceptualise the literature concerning maternal ED and child outcomes discussed in this literature review, Figure 1.4 outlines a model depicting the interplay between the biological, psychological and social factors arising from a maternal ED, which in combination with child factors may increase the risk of certain vulnerabilities in their children.

Figure 1.4: Biopsychosocial model of maternal eating disorders and childhood outcomes



As discussed throughout this literature review, pre-natal maternal eating pathology and co-morbid psychopathology can alter the intrauterine environment, increasing the risk of obstetric complications and stress regulation in their offspring, which may impact on child development. In the post-natal period, maternal sensitivity to their child's weight and shape combined with restrictive feeding may have direct implications for their child's diet and growth. These psychological and biological factors are likely to interact with genetic and social factors (e.g. marital discord), and child factors to increase the risk of vulnerabilities to development in their children.

1.13.1 Summary and gaps in the literature

This overview of the literature highlights the current understanding of associations between maternal ED and fertility, pregnancy, and child outcomes. ED are clearly associated with endocrine abnormalities, coupled with difficulties with relationships compromised fertility may be expected. However, investigations of fertility in women with ED continue to show conflicting results and further research in larger epidemiological studies is required.

While ED symptoms tend to reduce in pregnancy the risk of obstetric complications is elevated. Potential mechanisms for obstetric complications, such as pre-natal stress and nutrition, have not been investigated in women with ED.

Children of women with ED also have an increased risk of certain vulnerabilities in childhood, such as poor diet and growth problems. Studies of growth and diet in children of mothers with ED are typically limited to early infancy. Therefore, further investigation of growth and diet in later childhood, utilising larger sample sizes, is necessary. One area that has not been adequately investigated is stress regulation in children of women with ED, which may be influenced by pre- and post-natal factors and have consequences for later development.

Chapter 2. General Aims and Methodology

2.1 Chapter overview

This chapter provides an overview of the general aims of this thesis generated from the literature review presented in the previous chapter, followed by a description of the general methodology used to address these aims. In order to investigate the specific aims of this thesis, two separate methodological approaches are utilised within two samples: the Avon Longitudinal study of Parents and Children (ALSPAC) and Nutrition and Stress in Pregnancy (NEST-p). Finally, methodological issues pertaining to this thesis as a whole (e.g. statistical analyses, ethical approval and attrition) are outlined. Specific participant characteristics, details of the measures and procedures used will be discussed in the relevant results chapters.

2.2 General aims

The overall aim of this thesis was to investigate the effects of maternal ED on fertility, and pregnancy, as well as particular outcomes in their infants and children. A hypothesis driven approach was used, based on the literature described in Chapter 1, to investigate specific aspects of fertility, psychopathology during pregnancy and infant outcomes (stress regulation, diet and growth) in women with ED and their children, using both a general population cohort and prospective case-control design. Five studies are outlined in this thesis to achieve the overall aims. The general aims of each study are outlined below, specific aims and hypotheses are presented in the relevant results chapters.

Study one: Fertility and Pre-natal Attitudes towards Pregnancy in Women with Eating Disorders (Chapter 3)

The aim of study one was to investigate the length of time taken to conceive, feelings towards pregnancy and the prevalence of unintentional pregnancies in women with lifetime ED, compared to women without ED, in a large prospective population-based cohort.

Study two: Dietary Patterns and Macronutrient Intake in Children of Mothers with Eating Disorders (Chapter 4)

The aim of this study was to explore different dietary patterns and macronutrient intake in children of women with ED, compared to children of women without ED, in a longitudinal fashion between three and nine years, using a large prospective population-based cohort.

Study three: Growth Trajectories in Children of Mothers with Eating Disorders: A Longitudinal Investigation (Chapter 5)

The aim of this study was to explore differences in growth trajectories (between birth and ten years) in children of women with ED, compared to children of women without ED and children of women with other psychiatric disorders, in a large prospective population-based cohort.

Study four: Maternal Psychopathology and Stress in Pregnancy (Chapter 6)

The overall aim of this study was to investigate maternal psychopathology (ED symptoms and behaviours, depression and anxiety) and stress (perceived stress and diurnal cortisol rhythms) during pregnancy in women with active and remitted ED, compared to a healthy control group. Furthermore, this study aimed to explore the relationship between maternal psychopathology and cortisol levels during pregnancy in these three groups of women.

Study five: Birth Outcomes and Infant Stress Regulation in Infants of Women with Eating Disorders (Chapter 7)

The overall aim of this study was to examine obstetric complications and perinatal risk factors, e.g. maternal psychopathology, perceived stress and cortisol, for adverse birth outcomes in women with active and remitted ED. Additionally, differences in infant cortisol levels and response to a stressful situation were explored in infants of women with active and remitted ED, compared to a healthy control group.

2.3 Methodology

In order to address these aims and hypotheses two methodological approaches will be employed. The two methodological approaches outlined in this chapter were deemed most appropriate to address the individual aims of the respective research chapters. As

highlighted in the Literature Review, the majority of previous studies of women with ED and their children are subject to a number of biases since they are often derived from small investigations of participants at a single time-point drawn from clinical samples, and frequently lacked control groups. Therefore, the ability to generalise the findings of these studies is greatly limited. In order to overcome some of the methodological flaws of previous studies, data from Avon Longitudinal Study of Parents and Children (ALSPAC; a large prospective birth cohort) is utilised to investigate some of the specific aims of this thesis.

Despite the clear advantages of employing a large population-base sample to investigate research questions, data pertaining to specific research questions are not always available. Therefore, for the purpose of this thesis, where data were not available within ALSPAC, a clinical sample was recruited in order to carry out a pilot investigation of specific research questions arising from the literature review.

2.4 Avon Longitudinal Study of Parents and Children

2.4.1 Study overview

ALSPAC, also known as 'The Children of the 90s, is a longitudinal population-based study of over 14,000 women and their children, which was established in the early 1990s (www.alspac.bris.ac.uk). The overall objective of the study is to understand how the physical and social environment interacts with genetic determinants to affect health, development and behaviour over time (Golding, 2004; Golding, Pembrey, & Jones, 2001).

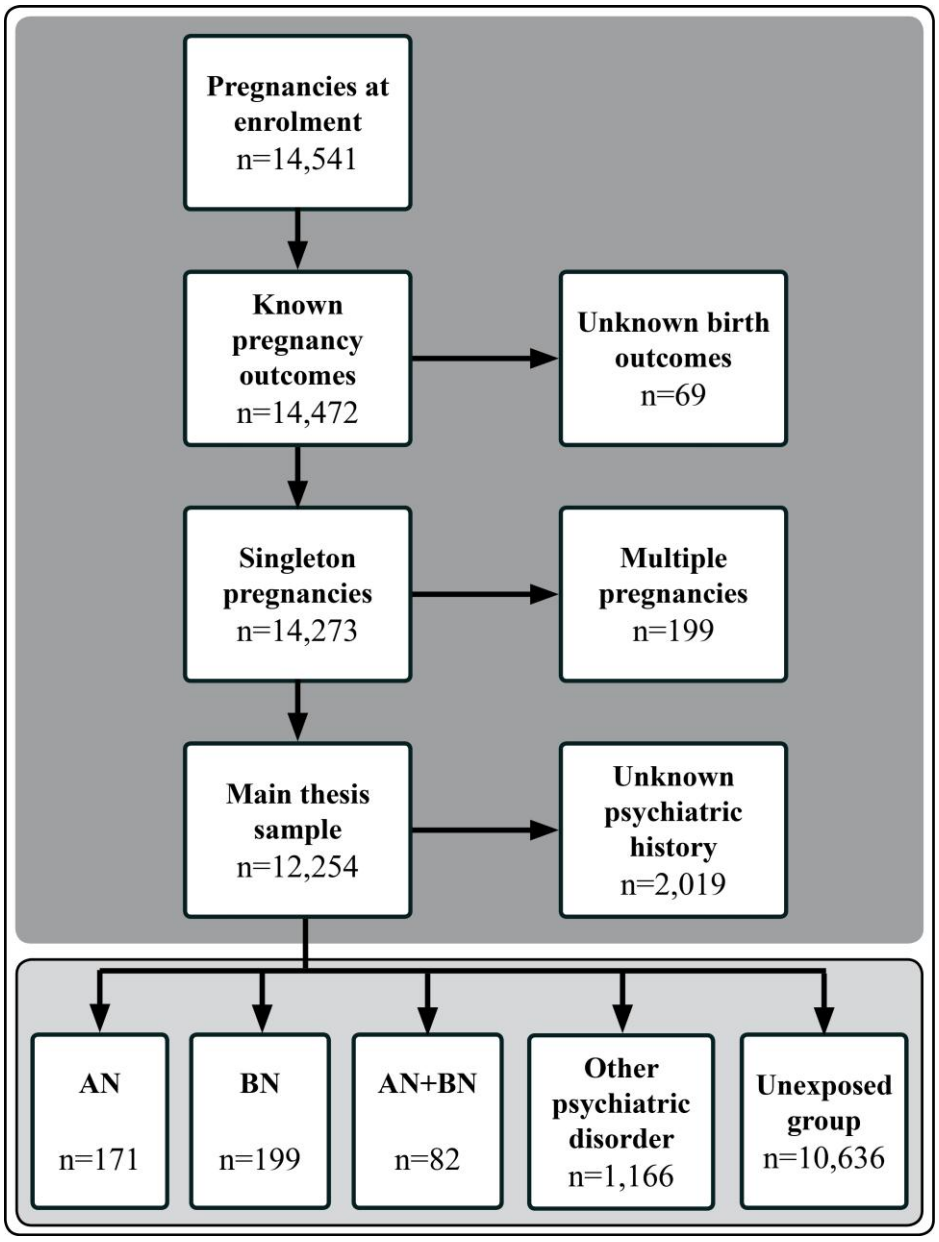
Participants were recruited from the geographical area formerly known as Avon, around Bristol in the south west of England. In the early 1990s Avon had a population of around one million people, relatively low migration and a mixture of social backgrounds and housing type.

2.4.2 Participants

The core ALSPAC sample consists of 14,541 pregnancies with 14,676 foetuses. This is the number of pregnancies for which the mother enrolled in the ALSPAC study and had either returned at least one questionnaire or attended the first "Children in Focus" clinic Of the initial 14,676 foetuses, 14,062 were live births (614 were early or late

miscarriages) and 13,988 were alive at 1 year. Out of the initial 14,541 pregnancies, all but 69 had known birth outcomes. Of these 14,472 pregnancies, 195 were twin, three were triplet and one was a quadruplet pregnancy, the remaining 14,273 had singleton pregnancies. Figure 2.1 displays a breakdown of the core ALSPAC sample investigated in this thesis.

Figure 2.1: ALSPAC Participants



Inclusion and exclusion criteria

All pregnant women living in the area formally known as Avon, excluding the city of Bath, with an expected delivery date between April 1991 and December 1992, were

eligible for enrolment in the study. Women who enrolled in the study but moved shortly after enrolment were excluded from follow-up.

For the purpose of the studies included in this thesis only singleton pregnancies were eligible for inclusion due to differing developmental trajectories from multiple pregnancies (n=14,273). Women were also excluded if they had not answered the 12 weeks questionnaire asking about maternal ED and psychiatric history (n=2,019), see Figure 2.1.

Sample characteristics and representativeness

It has been estimated that 85-90% of the eligible population took part in ALSPAC (Golding, et al., 2001), and that the sample is broadly representative of Great Britain as a whole (Baker, Morris, & Taylor, 1997). In order to assess the representativeness of ALSPAC, participants completing questionnaires at eight months post-partum were compared to mothers with infants less than one year of age in: the whole of Great Britain, from the 1991 census; and in the population of Avon in 1970 (Baker, et al., 1997). As indicated in Table 2.1 women included in the ALSPAC sample were more likely to own a property, own a car and to be married. Furthermore, there was a slight under-representation of ethnic minorities in the sample. Therefore, although broadly representative of the whole of Great Britain and Avon, participants in the ALSPAC are slightly under-representative of families from less affluent backgrounds.

Table 2.1: ALSPAC Sample Characteristics and Representativeness [5]

	ALSPAC Sample (%)	**Avon (%)**	**Whole of Great Britain (%)**
Owner occupied	79.1	68.9	63.4
1 + person/room	33.5	26.0	30.8
Car in household	90.8	83.7	75.6
Married Couple	79.4	71.7	71.8
Non-White Mother	2.2	4.1	7.6

Further investigation has been conducted in order to assess the representativeness of ALSPAC participants' early child growth. Accordingly, a comparison of the measurements taken at birth, and the one and two year clinics were compared to published growth standards in the UK in 1990. This investigation concluded that these growth measurements taken in ALSPAC were very similar to the general UK population (Baker, et al., 1997).

2.4.3 Materials and measures

The data collected by the ALSPAC research team prior to use in this thesis was derived from a variety of sources. For the purpose of this thesis four sources of information are utilised:

1. Self-completion questionnaires from mothers;
2. Record linkage to routine information: medical, educational and other records;
3. 'Children in Focus' - individual assessments of a randomly selected 10% sample at an ALSPAC clinic, at regular intervals from ages 4 months to 5 years.

[5] Table adapted from www.alspac.bris.ac.uk

4. ALSPAC clinics: from 7 years onwards the whole ALSPAC sample was invited to attend individual assessments at clinics.

Maternal data collection

Subsequent to enrolment in ALSPAC, information was collected from participants from early pregnancy onwards. During pregnancy mothers received four questionnaires appropriate to their gestational age. Table 2.2 highlights the data extracted from the pregnancy questionnaires that are utilised throughout this thesis.

Maternal psychiatric history

At 12 weeks gestation women were asked if they had any recent or past history of psychiatric problems: severe depression, schizophrenia, alcoholism, AN, BN or any other psychiatric disorder, in the "Your Pregnancy" questionnaire. Participants were asked: "have you ever had": "anorexia nervosa" or "bulimia nervosa", for each ED classification they were given the choice of "recent or past". These data were obtained by maternal self-report and was available on 83.5% of the sample.

Table 2.2: ALSPAC Maternal Pregnancy Questionnaires

Questionnaire	**Time-Point (Weeks)**	**Responses used in this Thesis**	**Response Rate**
Your Environment	8 weeks gestation	Relationship status	13,548
About Yourself	12 weeks gestation	Self-reported psychiatric problems (including ED)	12,452
		Fertility problems	
		Length of time to conceive pregnancy	
Having a Baby	18 weeks gestation	Feelings towards pregnancy	13,194
Your Pregnancy	32 weeks gestation	Socio-demographic information	12,423

Socio-demographic data

Socio-demographic information used throughout this thesis as covariates was obtained from the mother via self-report. The majority of this information was derived from the "your pregnancy" questionnaire, completed by participants at 32 weeks gestation. The variables used, how they were prepared and the corresponding response rates are outlined below:

- Maternal age - the age of the mother at delivery was calculated using the difference between the mother's date of birth and the offspring's date of birth.

  For the purpose of this thesis this value was kept as a continuous variable. These data were available on 100% of the participants.

- Ethnicity - at 32 weeks mothers were asked at to describe their ethnicity. The ethnic origins of the mother were obtained using the format derived from the 1991 United Kingdom Census. The categories provided were White, Black/Caribbean, Black/African, Black/other, Indian, Pakistani, Bangladeshi, Chinese and Other Specified.

  The majority of mothers, 95.2%, described themselves as white; therefore this variable was dichotomised into 'White' and 'Other Ethnicity' (i.e. all other ethnic groups). These data were available on 93.7% of the ALSPAC participants.

- Parity - at 18 weeks gestation mothers were asked about the number of previous pregnancies, miscarriages, live and stillbirth they had. Parity was defined as the number of previous pregnancies resulting in either a live-birth or a stillbirth.

  Parity was dichotomised into *primiparae* versus *multiparae.* These data were available on 100% of the ALSPAC participants.

- Maternal education – at 32 weeks gestation mothers were asked to provide details of their highest educational level, which was obtained from a five point education scale was with the following categories: CSE/No qualifications, vocational, O-Level or equivalent, A-level or equivalent, University degree.

Women who left the question blank were included in the lowest level, and only those who ticked 'not known' were coded as missing. This variable was dichotomised into qualification up to and including O-levels or equivalent versus A-level or equivalent and above. These data were available on 94.2% of the ALSPAC participants.

- Child gender - child gender was obtained from notification at birth. This variable was a dichotomised variable: male and female, and was available on 100% of the ALSPAC participants.

- Smoking – in a questionnaire sent to participants at 6 months post-natal ('My Son/My Daughter') participants were asked if they regularly smoked during pregnancy, and were given five possible responses: no, yes cigarettes, yes cigars, yes pipe, and yes other.

  For the purpose of this thesis this variable was dichotomised in to any smoking during pregnancy versus no smoking during pregnancy. Data on this variable were available on 100% of the ALSPAC participants.

- Maternal BMI - At 12 weeks in pregnancy, women were asked about their pre-pregnancy weight and height. From this information, a categorical pre-pregnancy BMI was derived as weight/height squared. These data was available on 92.7% of women.

- Household income – at approximately 47 months post-natal mothers were asked to specify their household income (including social benefits), per week. Participants were asked to choose from four possible responses: less that £100, £100-£199, £200-£299, £300-399 and more than £400 per week. These data were available on 89.9% of the ALPSAC sample.

- Gestational age at delivery – following delivery gestational age was recorded from mothers estimated due date based on their last menstrual period. For all infants that were delivered after twenty weeks, if there was any suggestion that the gestation was pre-term obstetric records were checked by a Professor of Obstetrics and Gynaecology for accuracy.

For the purpose of this thesis, this variable was kept as a continuous variable and was available on 100% of the ALSPAC participants.

Child data collection

Child data collected from ALSPAC is used in Chapter 4 and Chapter 5 of this thesis. The child data used throughout in these chapters were taken from four main sources:

1. Questionnaires completed by the study child's mother;
2. Direct measurements from clinics on a random 'children in focus' 10% of the sample;
3. Direct measurements from ALSPAC clinics;
4. Linkage to information from health visitor records.

ALSPAC clinics

During the last six months of recruitment of eligible mothers a random 10% of the sample was selected to form a group of children known as 'Children in Focus'. From the age of seven onwards all children involved in ALSPAC were invited to attend the clinic. The aims of these clinics were: to obtain information that could not be measured accurately through questionnaires and to validate self-reported measurements. The 'Children in Focus' group was seen at 4, 8 and 12 months and 1.5, and 2, 2.5, 3, 3.5, 4 and 5 years of age. Height and weight were measured at each visit. From the age of seven years onwards all the study children were invited for an annual assessment.

Specific details of the child measures used to assess the ALSPAC children's growth and diet, as well as how the data was handled are included in the relevant chapters (Chapter 4 and Chapter 5).

Validation of measures

The questionnaires used in ALSPAC underwent several design phases as part of the European Longitudinal Study of Pregnancy and Childhood (ELSPAC). The questionnaires were piloted with 100 parents (mothers and partners) at age-appropriate time-points (e.g. pre-natal and post-natal). The wording of the questionnaires was amended where confusion arose. Furthermore, a parental and young infant advisory group was formed who examined early drafts of all questionnaires. Validation of the

questionnaires was attempted by comparing self-reported questionnaire data with medical records, in particular self-completed psychological scales were compared to results from clinical interviews (Golding, et al., 2001).

2.4.4 Procedures

Recruitment

A wide variety of methods were used to attract potential eligible participants. The ALSPAC study was widely advertised via posters inviting potential participants to get in contact with the study team. Posters were displayed in places where it was anticipated that women in early pregnancy would be, such as: General Practitioner (GP) waiting areas, chemists, ante-natal clinics, and playschool and toddler groups. All eligible participants were also given information about the study at their initial meeting with a midwife. In addition, ALSPAC received substantial media coverage through the radio, television and newspapers, both locally and nationally.

Potential participants were asked to complete a card to return to the study team with their: name, address, last menstrual period (LMP) and estimated due date (EDD). Once women had expressed an interest in the study they received a brochure from the study team outlining the details of the study. The brochure informed women: that they were not obliged to take part in the study and could withdraw from it at any stage, that the information they and their child provided would be confidential and would not be linked to their names or addresses. Women were informed in the brochure that it would be assumed they wished to take part unless they informed the study team otherwise.

Approximately seven days after participants had received an ALSPAC brochure; eligible participants who had not expressed that they did not want to take part received the first questionnaire, appropriate to their gestation when they enrolled. For questionnaires administered during pregnancy a reminder letter was sent if a response had not been received within seven days, and a second letter was sent after ten days. If no response had been received within one month a member of the study team rang or visited the mother at home to assist with completion of the questionnaire.

Data preparation

The data used throughout this thesis had undergone differing levels of preparation prior to receiving it. Data preparation specific to the investigations undertaken in this thesis, will be discussed in the respective chapters.

Once questionnaires had been returned they were coded by undergraduate students from Bristol University, who were closely supervised. Each question was checked to ensure that there was not more than one ticked response, and that any comments made by participants did not alter the ticked response. Each variable had a coding rule for how to interpret problems such as multiple ticking or rounding of ages. All coding was cross-checked by a second person and then keyed and verified.

Eating disorder classification

As outlined above, at 12 weeks gestation women were asked if they had any recent or past history of psychiatric problems including AN and/or BN. Of the respondents, 460 women (3.7%) answered yes to either question; 117 women (1.4%) responded yes to ever having AN; and 199 (1.6%) women responded yes to ever having BN. Eighty-two women (0.7%) responded positively to both questions. Seven women (0.06%) reported a recent episode of AN and 51 (0.4%) reported a recent episode of BN.

In a previous doctoral thesis, Micali (2009) sought to validate maternal self-reported ED classification of AN or/and BN by comparing this data to lifetime ED behaviours (e.g. self-induced vomiting and laxative use) and cognitions (e.g. shape and weight concern) reported by mothers at 12 and 18 weeks gestation. This exploratory investigation revealed that women reporting a history of AN had a lower pre-pregnancy BMI, and a significantly higher history of self-induced vomiting (23.4%) and laxative use (29.1%), compared to women reporting other psychiatric illnesses and the general population.

Women reporting lifetime BN had a BMI within the normal range, comparable to the remaining sample. Over half of the women reporting BN (56.3%) reported self-induced vomiting (SIV) and nearly a third had used laxatives (29.1%). High rates of SIV (62.2%) and laxative use (55%) were also common in women who responded positively to both having AN and BN in their lifetime (AN+BN); furthermore these women had a lower pre-pregnancy BMI to the remaining sample.

Distinct ED characteristics between the groups, e.g. low BMI and prevalence of SIV, may have differing implications for the outcomes investigated within this thesis, therefore in all statistical analysis these groups will be maintained as three distinct groups of ED and compared to the unexposed group. Given the higher levels of ED cognitions and behaviours in the women reporting AN or/and BN from the remaining sample the self-reported ED classification was, in general, deemed to be relatively valid (Micali, 2009). Given the differences between the groups it was decided to keep the categories of women reporting a lifetime history of AN, BN or both (AN+BN) as three separate groups for the investigations included in this thesis. Furthermore, the classification of women reporting both AN+BN were kept separate due to the higher levels of lifetime laxative use and SIV compared to women with AN or BN only. Information on restricting and binging was not available; therefore these group classifications were considered most appropriate for the analysis used in this thesis. The grouping of participants used throughout this thesis is depicted in Figure 2.1.

Comparison groups

In order to investigate the aims of this thesis, the ALSPAC research chapters employ two comparison groups: women from the general population (unexposed group) and women reporting a psychiatric disorder other than an ED (other psychiatric disorders).

In all ALSPAC research chapters, women with ED or their children were compared to women or children without a history of an ED or any other psychiatric disorder. In total, 10,636 women responded that they did not have recent or past psychiatric disorder, this group forms the unexposed group used throughout this thesis.

The "Your Pregnancy" questionnaire, administered at 12 weeks gestation, also enquired about a recent or past history of psychiatric problems, including: depression, schizophrenia, and alcoholism. A total of 1,166 (9.5%) responded positively to having a lifetime history of a psychiatric disorder other than an ED. Of these women: 47 reported a history of drug addiction, 85 reported alcoholism, 4 women reported schizophrenia, 954 severe depression and 234 reported other psychiatric problems. In order to address the specific aims of Chapter 5, children of women reporting other psychiatric disorders are also included in the analyses.

2.4.5 ALSPAC: general methodological considerations

There are several general methodological considerations pertaining to the use of ALSPAC to investigate the aims and hypotheses of the investigations in this thesis, which are discussed below. More specific methodological considerations, strengths and weaknesses will be discussed throughout this thesis in the relevant results chapters.

The majority of previous studies on the topics investigated in this thesis are limited by small sample sizes, which are often drawn from clinical populations and lack a comparison group. Therefore, one of the main advantages of ALSPAC is its large sample size, which is representativeness of Avon and comparable to the UK. In order to replicate and further investigate the hypotheses generated from previous studies, research utilising large community samples is crucial. Furthermore, research in large community based cohorts has advantages over previous investigations, since cohorts are less prone to the selection bias that arises from investigations in small clinical samples.

ALSPAC contains substantial information on potential confounders and mediator variables, which have been lacking in previous investigations. Where appropriate relevant confounders and mediating variables will be included in analysis, therefore reducing the risk of type I errors.

The main limitation arising from investigating maternal ED in this sample, is that classification of maternal ED was based on self-report (AN, BN or both), which may be subject to bias. The exact relationship between participants' self-reported classification and DSM ED diagnosis (American Psychiatric Association, 2000) is therefore unclear. However, there is evidence that self-reported ED classification, when used in community studies, is comparable to many ED screening instruments (Keski-Rahkonen, et al., 2006). Moreover, behavioural data in the sample, described above, lend weight to the self-reported diagnosis (Micali, 2009; Micali, Treasure, et al., 2007b)

Nevertheless, consideration of the nature and suitability of the ALSPAC sample is necessary prior to investigation and interpretation of the findings in this thesis. In ALSPAC the self-reported prevalence of lifetime ED is 3.7%; 1.4% and 1.6% for AN and BN respectively, which is slightly higher than previous reports of ED in women of childbearing age. Striegel-Moore et al (2006) reported the prevalence of AN to be between 0.2–1.5% and the prevalence of BN to be between 0.4-0.8%. The prevalence of

ED was reported to be about 5% when partial ED were accounted for. It is therefore possible that some women in ALSPAC, if diagnosed by diagnostic interview, may have be more appropriately classified as EDNOS or a more sub-clinical ED, rather than full AN or BN. Furthermore, BED was not enquired about in the ALSPAC questionnaire. Nevertheless, other epidemiological studies have reported more similar prevalence of ED to those reported in the ALSPAC sample, for example Keski-Rahkonen and colleagues (2009; 2007) reported prevalence of 2.2% and 2.3% for AN and BN, respectively.

Despite the overall large sample size of ALSPAC, the number of women within each of the ED groups, particularly the AN+BN group, are relatively small, and investigations may therefore lack power to detect differences in the outcomes studied, and increase the risk of type II errors.

Furthermore, maternal ED classification in ALSPAC was based upon a lifetime history of an ED. Unfortunately, data on the exact timing and course of ED in these participants is currently unavailable and it therefore it is not possible to map the course of maternal ED symptoms and behaviours on to the outcomes investigated within this thesis.

2.5 Nutrition and Stress in Pregnancy Study

2.5.1 Study overview

The Nutrition and Stress in Pregnancy (NEST-p) study is an observational prospective study of pregnant women and their babies. The overall aim of this study is to examine the *in utero* mechanisms and pathways which may account for adverse perinatal and infant outcomes in the infants and children of women with past or active ED, by examining the potential relationship between maternal stress, nutrition and psychopathology and obstetrics and infant outcomes.

2.5.2 Participants

For the purpose of this thesis a core sample of 88 women were recruited during pregnancy. Participants were recruited from: Women's Services at King's College Hospital (KCH) in South London, Perinatal Psychiatry services and specialist ED services within the South London and Maudsley NHS Foundation trust (SLaM), between April 2009 and September 2011. See section 2.5.4 (Procedures) for details of

recruitment. Participants received a £10 gift voucher for participation in this study and travel expenses incurred on assessment visits were reimbursed.

Women were recruited to from three groups, those with an active ED during pregnancy (current ED group), those with a past history of an ED (recovered ED group) and a healthy control group. Of the 88 participants, 27 women were recruited to the current ED group, 26 to the recovered ED group and 35 to the healthy control group.

From the 88 women recruited during pregnancy, a sub-sample of mother and infant dyads (n=59, 67%), who's infants were 8 weeks post-natal prior to September 2011 were followed up in the post-natal period.

Inclusion and exclusion criteria

Cases: Inclusion criteria for the current and recovered ED group were women: with an active or past DSM-IV diagnosis of ED, between the ages of 18-45, and pregnant within the first or second trimester of pregnancy. Women experiencing co-morbid psychiatric illness were included in the current ED group, with the exception of psychotic illnesses, who were excluded. In order to minimise the effect of confounding from active psychiatric illness, women with a past ED diagnosis but an active other psychiatric disorder (such as depression and anxiety) were excluded. Furthermore, women were excluded if they suffered from any chronic medical disorder (pulmonary, cardiac, autoimmune or endocrine) or were unable to communicate in English.

Controls: Inclusion criteria for the healthy control group included, no active or past psychiatric disorder including ED, between the ages of 18-45 and pregnant within the first or second trimester of pregnancy. Women were excluded if they suffered from any chronic medical disorder (pulmonary, cardiac, autoimmune or endocrine) or were unable to communicate in English. Controls were excluded if they met criteria for a full or partial lifetime psychiatric illness.

2.5.3 Materials and measures

Maternal questionnaires

Eating Disorder Diagnostic Scale (EDDS)

An adapted version of the EDDS was used to assess eating pathology (Stice, Telch, & Rizvi, 2000). The EDDS is a 22 item self-report measure designed to replicate DSM-IV diagnostic criteria for AN, BN and BED within the last 'three' or 'six months'. Responses to questions enquiring about ED symptoms or behaviours are made on either a Likert scale, with a yes/no response, or in terms of frequency of ED behaviours. For the purpose of this thesis, in order to assess lifetime frequency of ED symptoms and behaviours an additional option of 'ever' to questions enquiring about frequency of ED symptoms was included in this questionnaire.

The EDDS has been shown to have good test-retest reliability, with kappa coefficients ranging from 0.71 to0 .95 (Stice, et al., 2000). The EDDS has been used to identify individuals meeting diagnostic criteria for ED and has shown excellent agreement with 'gold standard' diagnoses obtained from the Eating Disorder Examination Interview (κ = 0.74 – 0.93) (Stice, Fisher, & Martinez, 2004; Stice, et al., 2000)

Structured Clinical Interview for Axis I DSM-IV-TR Disorders (SCID-I)

The SCID-I (First, Gibbon, Spitzer, Williams, & Janet, 2002) is a semi-structured diagnostic interview used to determine Axis-I DSM-IV-TR disorders (American Psychiatric Association, 2000). It can be used with both psychiatric and general populations, over the age of 18. The research version of the SCID-I was used to determine the following: mood disorders, substance use disorders, anxiety disorders and eating disorders.

The SCID-I provides a series of open questions designed to enquire about the presence or absence of DSM-IV criterion items. Although most of the questions can be answered with a simple yes or no, prompts are used throughout to encourage participants to elaborate until the interviewer has elicited enough information to determine whether a criterion has been met or not. With the exception of Generalised Anxiety Disorder (GAD) the SCID-I can be used to determine whether Axis-I diagnostic criteria has been met lifetime or whether there is a current episode. The SCID-I guidelines suggest that

symptoms of a current ED should be met within the last month. For the purpose of this thesis, and due to fluctuations of ED symptoms during pregnancy, the 'current ED criteria' was slightly changed to include symptoms within the three months prior to pregnancy.

The SCID-I is widely used in research to determine DSM diagnoses. The test-retest reliability has recently been reported to have kappa coefficients between 0.70 and 1.0 (First, et al., 2002). Test-retest reliability for the use of the SCID-I to diagnose ED have been reported to range between 0.61-0.77 (Lobbestael, Leurgans, & Arntz; Zanarini, et al., 2000). Given the lack of other gold standard measures of psychiatric diagnoses studies investigating the validity of the SCID have rarely been undertaken. In order to ensure inter-rater reliability within the investigations presented in this thesis, maternal diagnosis was discussed on a monthly basis in team meetings.

Eating Disorder Examination Questionnaire (EDE-Q)

The EDE-Q (EDE-Q; Fairburn & Bèglin, 1994) is a 36 item self-reported questionnaire focusing on ED symptoms and behaviours within the last 28 days. In addition to a global EDE-Q score, four sub-scores can be derived from the scale relating to: dietary restraint, eating concerns and concerns about weight and shape. Frequencies of ED behaviours (binge eating and compensatory behaviours) are assessed in terms of the number of episodes occurring during the past 28 days.

In community samples, the EDE-Q has been found to have good internal validity and test-retest reliability (with Pearson's r ranging from 0.54-0.92 on EDE-Q subscales) (Luce & Crowther, 1999). Good concurrent validity (with correlations with EDE subscales ranging from 0.68 to 0.78); acceptable criterion validity, and good sensitivity (0.83) and specificity (0.96) to identify cases, has also been demonstrated for the EDE-Q (Mond, Hay, Rodgers, Owen, & Beumont, 2004).

Becks Depression Inventory (BDI)

The BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) is a 21 item multiple choice self-reported measure of the intensity and severity of depression. Questions relate to how the respondent has felt within the last week. Participant scoring between 1-10 are considered to be experiencing 'normal ups and downs'; 11-16 'mild mood

disturbances'; 17-20 'borderline clinical depression'; 21-30 'moderate depression'; 31-40 'severe depression' and over 40 'extreme depression'.

The reliability and validity of the BDI has been extensively investigated, and good concurrent validity has been consistently demonstrated (Richter, Werner, Heerlein, Kraus, & Sauer, 1998). The reliability of the BDI has also been confirmed by numerous studies in psychiatric and community samples, with most researchers reporting alpha coefficients above 0.75 for internal consistency (Beck, Steer, & Carbin, 1988). The test-retest reliability of the BDI has been shown to be dependent on the time between measurements, and has been found to be higher in psychiatric compared to non-psychiatric samples (Richter, et al., 1998). The BDI is frequently used to assess depression in pregnant populations (Lancaster, et al., 2010), and has been found to have good sensitivity (0.90) and specificity (0.78) during pregnancy, and in the post-natal period (sensitivity = 0.81; specificity=0.80) (Ji, et al., 2010).

Spielberger State-Trait Anxiety Inventory (STAI)

The STAI is a frequently used measure for self-reported anxiety (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). The STAI consists of two separate 20-item scales of anxiety: state anxiety (e.g. how do you feel right now), which is considered to be relatively temporary and transient, and trait anxiety (how do you generally feel), which is considered to be more longstanding and stable.

Good test-retest reliability and internal consistency of the STAI has been demonstrated. Test-retest reliability correlations, provided by Spielberger, were found to be 0.54 for the state anxiety scale and 0.86 for the trait anxiety scale (Spielberger, et al., 1983). Similarly, adequate construct validity to measure anxiety in exam situations (Spielberger, et al., 1983) and concurrent validity with DSM-IV diagnosis of GAD (Okun, Stein, Laurie, & Silver, 1996) have been demonstrated. The STAI is increasingly being used to measure anxiety during pregnancy and a preliminary investigation of construct validity (Gunning, et al., 2011), concluded that the STAI is appropriate for use in pregnant samples.

Pregnancy Related Anxiety Questionnaire Revised (PRAQ-R)

The PRAQ-R (Huizink, Mulder, Robles de Medina, Visser, & Buitelaar, 2004) used within this thesis is a shortened version of the 34-item PRAQ, developed by Van den

Bergh (Van den Bergh, 1990). The PRAQ-R is a 10-item self-reported measure of pregnancy specific anxieties. In addition to a global pregnancy related anxiety (PRA) score, three sub-scales can be distinguished: fear of giving birth, fear of bearing a physically or mentally handicapped child and concern about one's appearance.

Satisfactory internal consistency of the three sub-scales has been demonstrated during each trimester of pregnancy, with alpha values above 0.75 on all subscales. Pregnancy specific anxieties are thought to be distinct from more general anxiety or depression during pregnancy, and good discriminant validity of this scale has also been supported by factor analysis, which found pregnancy related anxiety to be distinct from measures of both general anxiety (STAI) and depression (Edinburgh Post-natal Depression Scale; EPDS) (Huizink, Mulder, Robles de Medina, et al., 2004). Furthermore, it has been demonstrated that PRA, rather than general anxiety, is more strongly related to birth outcomes and HPA axis functioning in pregnancy (Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999) than alternative measures of anxiety.

Perceived Stress Scale (PSS)

The PSS (Cohen, Kamarck, & Mermelstein, 1983) is a widely used measure of an individual's perception of stress, and the degree to which situations are deemed to be stressful. The PSS consists of ten items, enquiring about specific thoughts and feelings in the last month. Participants are asked to indicate how often they felt a certain way on a five point scale. The PSS has been shown to have good internal reliability (alpha coefficient = 0.78) (Cohen & Williamson, 1988) and to be predictive of a variety of health outcomes (Cohen, et al., 1983). However, given that perceived stress is influenced by daily hassles, life events and coping resources, the predictive validity of the PSS is thought to rapidly decrease after four to eight weeks (Cohen, et al., 1983). As such, test-retest correlations have been found to vary between 0.55 and 0.85, dependent on the duration of time between testing. Furthermore, perceived stress, as measured by the PSS, has been shown to be distinct from negative life events, demonstrating good discriminant validity (Cohen, Tyrrell, & Smith, 1993). An increasing number of studies have utilised the PSS in pregnant samples (e.g. Paarlberg, Vingerhoets, Passchier, Dekker, & Van Geijn, 1995), and increases in perceived stress across gestation have been found to be associated with shorter gestational length (Glynn, Schetter, Hobel, & Sandman, 2008).

Socio-demographic information

The following socio-demographic information was obtained via self-report:

- Maternal age – upon recruitment mothers were asked their date of birth, from this their age at recruitment was calculated as the difference between the two dates.

- Marital status – women were asked to provide their marital status at recruitment from four options: single, cohabiting, married or other. For the purpose of this thesis marital status was dichotomised in to single versus cohabiting/married.

- Ethnicity - women were asked to report their ethnicity, which were grouped under six headings: White, Mixed, Asian or Asian British, Black or Black British, and Chinese or other ethnic group. These six grouping have been used in the UK since April 2001 by the Department of Health as a National Standard to record the ethnic group of patients, services users and staff, and are identical to those used in the 2001 national census (www.dh.gov.uk). This variable was dichotomized into white ethnicity versus other ethnic background.

- Education – women were asked to report their highest level of education from four categories: no formal qualifications, GCSE/NVQ, A-Levels and higher education. This variable was dichotomised into no formal qualifications/GCSE/NVQ versus A-Levels/higher education.

- Parity – the number of previous pregnancies, live and stillbirths was recorded from maternal self-report at recruitment. Parity was defined as the number of previous pregnancies resulting in a live or still birth. Parity was dichotomised into *primiparae* versus *multiparae*.

- Pre-pregnancy height and weight – pre-pregnancy height and weight was recorded from maternal self-report at recruitment. From this a continuous variable of pre-pregnancy BMI (kg/m^2) was calculated.

- Current weight and height – at each visit weight and height was recorded by the visiting researcher. From this a continuous variable of BMI (kg/m^2) was

calculated for each visit. Gestational weight gain (kg) was calculated as the amount of weight gained between assessment visits.

- Smoking – women were asked at recruitment about their previous and current smoking. Participants were asked have you previously smoked (prior to this pregnancy) and do you currently smoke? Four options, relating to frequency of smoking were provided: none, 1-9 cigarettes a day, 10-19 cigarettes a day and more than 20 cigarettes a day. From this a dichotomous variable relating to pregnancy smoking was created: smoked in pregnancy versus never smoked in pregnancy.

Maternal salivary cortisol

In order to investigate physiological levels of stress during pregnancy, women were asked to provide saliva samples during pregnancy, from which concentrations of salivary cortisol were measured. In order to obtain saliva, participants were provided with six appropriately-labelled conical tubes (salivettes®) containing oral swabs for saliva collection, and instructed on how to take the samples.

As highlighted in the literature review, the HPA axis is one of the major stress systems, of which cortisol is the end product of a physiological response to stress. Cortisol has a diurnal rhythm, peaking approximately 30 minutes after wakening and characterised by low evening levels, which is maintained during pregnancy (de Weerth & Buitelaar, 2005). Disruption to the natural diurnal rhythm of cortisol is thought to reflect dysfunction of the HPA axis.

Collection of salivary cortisol is a relatively non-invasive method of obtaining cortisol levels. Furthermore, cortisol as measured in blood is bound to cortisol binding globulin, rendering it biologically inactive. Given the increase in cortisol binding globulin throughout pregnancy, unbound cortisol measured in saliva is thought to be a more valid measure during pregnancy (Buss, et al., 2009).

Infant salivary cortisol

Infant saliva was collected at routine immunisations at 8 weeks post-partum. Oral swabs as provided for maternal saliva collection are not suitable for children under the age of six years; therefore Sorbettes (eye sponges) were used for infant saliva collection. To

ensure an adequate sample, two Sorbettes were used together and then were placed in one conical tube for centrifugation.

Obstetric records

The following data was collected from obstetric records at the delivering hospital:

- Birth weight (grams) – was recorded by midwives at birth and extracted from medical records. From this a dichotomous variable indicating whether the delivery was of a low birth (<2500g) was calculated.
- Gestational age at delivery (weeks) – was calculated as the difference between participants estimated due date (from ultrasound scan) and their delivery date, and was extracted from medical records. From this a dichotomous variable indicating whether the delivery was premature (<37 weeks) was calculated.
- Delivery mode – women's mode of delivery (vaginal, elective/emergency caesarean, ventouse and/or forceps) was recorded and extracted from their delivery notes. From this a dichotomous variable indicating whether any intervention was required during the delivery vs. no intervention.
- Head circumference (cm) – was measured at birth by midwives and extracted from medical records.

2.5.4 Procedures

Recruitment

The three groups of participants (current ED, recovered ED and healthy control groups) included in this study were identified via four main recruitment methods:

1. Kings College Hospital (KCH) Obstetric Services: a random sample of women attending their first or second routine ultrasound scan (nuchal and anomaly), between 11 and 25 weeks gestation, were screened for ED symptoms using an adapted version of the EDDS (see section 2.5.3). At the end of the questionnaire women were invited to leave their contact details and indicate whether they were happy to be contacted by a member of the research team regarding the NEST-p study.

2. SLaM Perinatal Psychiatry Team: women referred to the perinatal liaison team at KCH for a past or active ED were identified by the clinical team, or a researcher attending weekly perinatal psychiatry team meetings, women expressing an interest in the study were contacted by a researcher and given details of the study.

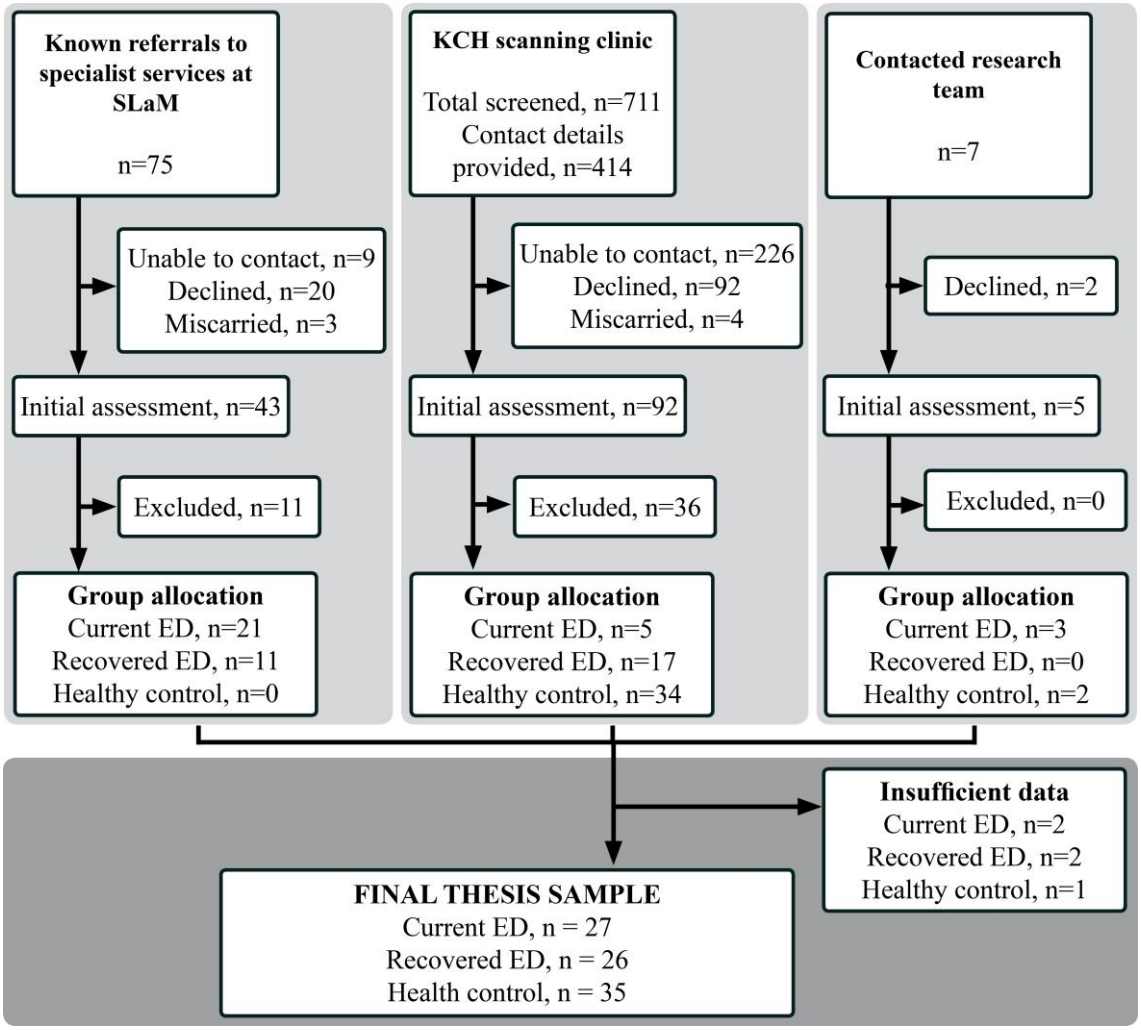
3. SLaM ED services: women who were in their first or second trimester were identified by clinicians involved in their treatment within ED inpatient and outpatient services. Those who express an interest in the study were contacted by a researcher and given details of the study.

4. Advertisements: Posters and leaflets were displayed in the obstetric services at KCH, perinatal psychiatry departments and SLaM ED services. Information on the study was also available on websites (http://public.ukcrn.org.uk and www.iop.kcl.ac.uk). Researcher contact details were provided on advertisements and volunteers approaching the researcher were eligible for inclusion in the study.

Participants with past or active ED during pregnancy were recruited via all four methods; healthy controls were recruited via method one and four only. Once participants had been identified and expressed an interest in taking part in the study they were provided with detailed information on the study protocol. An initial appointment was arranged in which written informed consent was obtained by the researcher. Following which women were interviewed to ascertain lifetime psychiatric disorder and medical history, to determine eligibility and group classification.

Figure 2.2 illustrates the number of referrals to specialist services at SLaM (via the ED and Perinatal Psychiatry teams) and the number of women screened for an ED at KCH ante-natal clinic. Details of how many women completed an initial assessment via each recruitment method and finally participants eligible for group allocation are highlighted.

Figure 2.2: Flow of NEST-p participants by recruitment source



Specialist services at SLaM: During the course of this PhD there were 75 known referrals to specialist ED and perinatal psychiatry services within SLaM. Twenty women declined to take part in the study, and it was not possible to make contact with a further nine women, three women had miscarried prior to being invited for an initial assessment. After completing an initial assessment 11women were not eligible for the current study: one lady was excluded due to diabetes, three women were excluded as they were referred too late in gestation or during the post-natal period, two women had a co-morbid psychotic disorder, one women was under the age of 18, two women were deemed not suitable to be approached for the study by the referrer, and two women had a past history of an ED but met criteria for current depression or anxiety disorder.

Women's Health Services at KCH: During the course of this PhD 711 women were screened for an ED using the EDDS. Of these women 414 left contact details and agreed to be contacted. It was not possible to make contact or arrange an initial appointment with 226 women, a further 92 women were contacted and declined to take part in the study, and four women had miscarried or had a stillbirth by the time they were contacted. Initial screening assessments were carried out with 92 women; of these women 36 were excluded. Nine women were living or moving out of area, 13 women were unable to communicate sufficiently in English, and 14 women were excluded due a current or past medical disorder, or because they met criteria for a full or partial psychiatric disorder.

Following the initial assessment a total of 93 women were allocated to one of the three groups for the study. Of these 93 women five participants provided did not have sufficient data to be included within the investigations undertaken in this thesis and therefore were excluded from these studies.

Participant groups

Past and current psychiatric diagnoses were determined using the SCID interview, and eligible participants were allocated to one of three groups; twenty-seven women met criteria for an active ED (current group), 26 women met criteria for a past ED (recovered) and 35 women had never met criteria for an ED (healthy control group). Full diagnosis for an ED (AN, BN or EDNOS) was made on the bases of symptoms at assessment and three months prior to pregnancy.

For diagnoses of a current ED participants were required to meet DSM criteria for an ED either during pregnancy or in the three months prior to their pregnancy. Although the number of participants in this sample does not allow for analyses between diagnostic classifications, participants lifetime diagnoses was recorded and descriptive data are presented in results sections of this thesis where appropriate. Lifetime diagnosis was based upon the duration and reoccurrence of AN, BN and EDNOS according to full DSM-IV ED criteria (American Psychiatric Association, 2000). Within the current group, 12 women met full criteria for lifetime AN (four with AN-R and eight with AN-BP), eight met criteria for lifetime BN, and four women met lifetime criteria for EDNOS (three met criteria for BED and one for EDNOS-AN type).

A group of participants whose ED had remitted prior to their current pregnancy were recruited in order to investigate: 1) whether pregnancy and infant outcomes in women with ED are specific to women with active ED, and 2) the potential risks associated with a past history of an ED during pregnancy and in the early past-natal period.

For the investigations presented within this thesis, participants from the NEST-p study were considered to have recovered from their ED if they did not meet DSM criteria for an ED in one or more years prior to their current pregnancy. Within the recovered group: four women met criteria for lifetime AN, eight met criteria for BN, and 14 EDNOS. Within the 14 women who met criteria for lifetime EDNOS, 10 women had EDNOS-AN type, two women met criteria for BED and two women met criteria for Purging Disorder.

Where descriptive statistics according to ED diagnostic classification are presented in this thesis from the NEST-p sample, three groups are defined in terms of broadly defined lifetime ED diagnoses, i.e. AN type (including lifetime EDNOS-AN type), BN type (including purging disorder) and BED.

Participant assessments

Following the initial assessments, eligible participants were invited to take part in two assessments during pregnancy, and one assessment with their infants at eight weeks post-natal.

Mid-pregnancy assessment: Baseline assessments took place during mid-pregnancy; women were visited at home or attended an appointment at the Eating Disorders Unit of the Institute of Psychiatry to complete the assessment. This assessment was conducted at a mean of 18 weeks gestation (s.d. 4.1). Maternal symptoms of ED, depression and anxiety were assessed using the: EDE-Q, BDI, and STAI, respectively. Pregnancy related anxiety and perceived stress were also assessed using the PRAQ-R and PSS.

Women were given saliva assessment packs to complete at home and provided with detailed verbal and written instructions of how to complete the samples, see below.

Late pregnancy assessment: Follow up assessment took place during ‘late pregnancy’ at a mean of 33.2 weeks gestation (s.d. 1.5). Following the same procedures as the ‘mid-pregnancy’ assessment, participants were asked to complete the: EDE-Q, BDI, STAI,

PRAQ-R and PSS questionnaires and provided with saliva assessment packs to complete at home and return by post once completed.

Salivary cortisol: At two time points during pregnancy (23-25 weeks and 30-32 weeks gestation) participants were provided with an assessment pack to collect salivary cortisol, which they were asked to complete at home. Diurnal salivary cortisol was measured on two separate occasions during pregnancy, on three occasions throughout the day (on awakening, 30 minutes following awakening and 8pm) on two consecutive days. Participants were provided with six appropriately-labelled conical tubes (salivettes®) containing oral swabs for saliva collection, and instructed on how to take the samples. Detailed written instructions were given to participants and provided verbally by the researcher.

At the appropriate times, participants were advised to gently chew the swab, repeatedly moving it around in their mouths for two minutes or until it was saturated with saliva. Once the swab had been completed they were advised to return it to the collection tube, without touching it with their hands, and to store in their fridge until all swabs had been completed. Participants were further advised not to eat, drink, smoke or chew gum for at least an hour before providing a saliva sample. For morning samples participants were asked not brush their teeth, have breakfast or any other drinks prior to providing the sample. Furthermore, participants were advised to collect saliva on days when they were free from a cold/flu or other infection symptoms and, if possible, when they did not have bleeding gums. Participants were also provided with a record sheet, and asked to record: their time of wakening, the exact timing of sample collection and to comment on any "hassles" (e.g. difficult conversations, arguments you had with friends etc.) or pain of any kind (e.g. headache, migraine, toothache) that had been experienced in the last half to one hour before providing the specimen.

Once all six samples had been completed, participants were asked to post the samples back to the research centre, in a pre-paid envelope, and to record the date of posting on the record sheet. When samples were received, they were immediately frozen and stored at Stress, Psychiatry and Immunology Lab (SPI-lab) at the James Black Centre, Kings College London, at -20° Celsius (C) until analysed.

Birth outcomes: Participants were contacted around the time of their estimated due date (EDD), and the date of birth of their baby recorded once they had delivered. Obstetric records were requested from maternity services and the details extracted from maternal scan notes and discharge summaries.

Eight week post-natal assessment: On the day of their infants eight week immunisations participants were visited at home and asked to complete the EDE-Q, BDI, STAI, and PSS questionnaires.

In order to assess infants stress response, infant cortisol levels were measured prior to and following their routine immunisations. This stress paradigm was selected for two predominant reasons. First, immunisations are a naturally occurring stressor of infants and therefore did not require any experimental manipulations, second infants cortisol response to painful stressors, such as immunisations, have been shown to more reliably elicit a cortisol response than other stress paradigms (Gunnar, Talge, & Herrera, 2009). Infant pre-immunisations swabs were completed by the researcher and demonstrated to the mother. A researcher attended the eight week immunisations and recorded details of the timings and completed a post-immunisation saliva swab with the infants 20 minutes following the immunisation.

Although the timing of peak cortisol values following a stressful event can vary considerably between individuals, a delay of 20 minutes following the immunisation was selected for this study as it is thought to represent typical peak cortisol levels in infants following a stressor (Gunnar, et al., 2009).

During this 20 minute period mothers were asked to avoid feeding their infant if possible. On the following day mothers were instructed to take samples from their infant at 8am and 8pm, following the procedures demonstrated by the researcher. Participants were instructed to avoid feeding their infant for 30 minutes prior to taking the sample, and to record any difficulties on the record sheet. Infant samples were stored by participants in their fridges, and returned by post to the research centre once all samples had been completed. Samples were frozen at 20°C until they were analysed. Record sheets were completed by participants, who were asked to record their time of wakening on both days, time of immunisations and exact timings of swabs, as well as details of any illness.

Salivary cortisol analysis

Saliva was recovered from the swabs in the salivettes® by centrifugation, and analysed by Patricia Zunszain at the Stress, Psychiatry and Immunology Laboratory (SPI-Lab), KCL: "determination of cortisol levels was carried out using the High Sensitivity Salivary Cortisol ELISA KIT from Salimetrics, following the recommended procedure. Briefly, 25µl of saliva and standards were assayed in duplicates, by incubation on a microtitre plate coated with monoclonal antibodies against cortisol. Cortisol linked to horseradish peroxidase was then added, to compete with cortisol in the standards and unknowns (saliva samples) for the antibody binding sites. The unbound components were then washed away. Cortisol peroxidase that bound was then measured by reacting the peroxidase enzyme with the substrate tetramethylbenzidine. The amount of cortisol peroxidase detected, as measured by the intensity of colour developed by reading its optical density, is inversely proportional to the amount of cortisol present. Optical density was read at 450nm with correction at 620nm, using a Beckman Coulter DTX 880 plate reader, with Multimode Detection Software 2.0.0.12 (Beckman Coulter Inc, CA, USA).

2.6 Statistical analyses

Specific details analyses conducted on the data collected as part of the ALSPAC and NEST-p investigations are described as appropriate in the relevant study chapters. Statistical analyses were conducted using SPSS versions 15.0.0 (SPSS Inc, 1999) and STATA version 11 (StataCorp, 2009). All statistical tests presented are two-tailed and the standard 5% level of significance was applied to determine initial group differences. Initial analysis was conducted for each of the studies undertaken in this thesis in order to investigate the characteristics of the data set and to check the underlying assumptions of the statistical test used, such as normal distribution.

2.6.1 Power calculations

ALSPAC: the statistical programme nQuery Advisor 5.0. was used to estimate the sample size required for the statistical analyses undertaken on the ALSPAC data, taking into account comparisons between ED and comparison groups. The range of power values accounts for comparisons of smaller groups and larger groups. With the available sample sizes and taking into account group sizes, small group differences in continuous

outcomes (effect sizes of 0.3) could be detected with a power of 75% to 93% at the 5% significance test level. Group differences in proportions for common outcomes could be detected with 92% to 99% power at the 5% significance test level. Group differences in proportions for uncommon outcomes could be detected with 63% to 99% power at the 5% significance test level.

NEST-p: The power calculations underpinning the recruitment for the NEST-p study were based on pilot data from a similar study on stress in pregnancy in depressed women a sample size of 20 "depressed women" and 36 "healthy controls" was sufficient to demonstrate differences in HPA axis hormones concentration in pregnancy at a $p<0.005$ level. Based on the same study 10 babies from "depressed" group and 15 babies from the "healthy control" group, will be required to give 80% power to detect differences in cortisol values at the $p<0.05$ level.

2.7 Attrition

In each investigation selective attrition was assessed, and is reported within the relevant results chapters. Two main approaches to handling missing data are employed throughout this thesis:

1. In cases of missing data due to partial responses on maternal questionnaires from the NEST-p study, a single imputation was made and subscale or scale scores from maternal questionnaires were prorated (Enders, 2010). This was achieved by multiplying the sum of scale by the number of items in the scale and dividing by the number items validly answered. Prorating was used if fewer than 15% of items in each scale or sub-scale were missing.

2. In cases where data was considered to be missing at random, multiple imputations were used. Specifically, switching regression, an iterative multivariable regression technique was used to impute the missing data. Five imputations were used to produce datasets without missing values, and the rules of Rubin (Rubin, 1987) were used to combine the estimates to obtain valid overall estimates.

2.8 Ethical approval

ALSPAC: The study was approved by the Institute of Psychiatry Ethics committee (Ref. 110/02) and the ALSPAC Law and Ethics committee and the Local Research ethics Committees.

NEST-p: This study was approved by The Joint South London and the Institute of Psychiatry NHS Research Ethics Committee' (Ref. 09/H0807/12).

Chapter 3. Fertility and Pre-natal Attitudes towards Pregnancy in Women with Eating Disorders

Parts of the chapter appear as a regular article in: British Journal of Obstetrics and Gynaecology [6,7]

3.1 Introduction

As outlined in Chapter 1 menstrual patterns and ovulation can be disrupted in women with ED. Furthermore, ED have been associated with differential patterns of sexual development and relationships difficulties. Therefore, compromised fertility may be expected. However, there has been insufficient research attempting to determine the extent of disruption to fertility in women with ED.

ED have been found to be common in women receiving fertility treatment (Freizinger, et al., 2008; Stewart, et al., 1990). However, as discussed in Chapter 1, studies investigating the frequency and prevalence of pregnancies in women with ED continue to show conflicting findings (Brinch, et al., 1988; Bulik, et al., 1999; Crow, et al., 2002).

The length of time taken to conceive is a more useful measure of fertility in epidemiological studies (Baird, Wilcox, & Weinberg, 1986; Joffe, 1997; Joffe, Villard, Li, Plowman, & Vessey, 1995). Most women will become pregnant within three to six months of trying to conceive, and up to 90% will become pregnant within 12 months of unprotected sex (Tietze, 1956). Infertility is often therefore defined as an inability to conceive for 12 months or longer (Hull, et al., 1985), however delays in conception time can reflect a whole range of underlying fertility problems.

Very little is known about the early relationship between mother and baby and pre-natal bonding in women with ED. A study by Koubaa found that as many as 90% of women

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[6] **Easter, A.,** Treasure, J., & Micali, N. (2011). Fertility and pre-natal attitudes towards pregnancy in women with eating disorders: results from the Avon Longitudinal Study of Parents and Children. *BJOG: An International Journal of Obstetrics & Gynaecology*.

[7] I presented the findings of this investigation at the 2010 Parental Brain Conference, Edinburgh, for which I received the 'Parental Brain Travel Award'.

with a history of ED report problems regarding their adjustment to motherhood at three months post-partum, compared to 13% of controls (Koubaa, et al., 2008). However, there is limited research within this area, particularly within large epidemiological samples. The mother-infant relationship begins during pregnancy, when the mother begins to bond with her unborn child (Stone & Menken, 2008) and prepare for birth and motherhood. Poor pre-partum bonding has been shown predict poor post-partum mother-infant attachment, which may ultimately have long-term consequences for both mother and child (Gipson, Koenig, & Hindin, 2008). Given the substantial bodily changes and inevitable weight gain during pregnancy, it may be a particularly daunting experience for women with ED. However, feelings about pregnancy have not been investigated in this group.

3.2 Aims and hypotheses

The aim of this study was to investigate fertility and feelings towards pregnancy in women with lifetime ED, compared to women without ED (unexposed group), in large prospective population-based cohort. Specifically this study aimed to investigate:

1. the length of time taken to conceive and rates of help and advice sought for fertility problems in women with ED, compared women without an ED;
2. the occurrence of unintentional pregnancies in women with ED compared to women without ED;
3. women's feelings towards their pregnancy at 12 and 18 weeks gestation in women with lifetime ED compared to women without a history of an ED;

Hypothesis under investigation:

1. Women with ED will take longer to conceive than unexposed women.
2. Women with ED will have a higher frequency of unintentional pregnancies compared to unexposed women.
3. Women with ED will feel more negative about their pregnancy.

3.3 Methods

3.3.1 Design and participants

This study is based on data collected from the Avon Longitudinal Study of Parents and Children (ALSPAC) (Golding, et al., 2001). Full details of the sample and group classification are outlined in the General Aims and Methodology (Chapter 2).

Women were excluded from the current study if they did not respond to the 12 week questionnaire (2,019). For the purpose of this study only included singleton live births (12,254) were included, and women who reported having had a psychiatric disorder other than an ED only (n=1,166) were excluded. Of the women included in the present study: 171 reported a history of AN, 199 reported a history of BN, and 82 reported a history of both AN and BN (AN+BN). Women not reporting a history of ED or other psychiatric disorder (n=10, 636) formed the 'unexposed' comparison group.

3.3.2 Outcomes and measures

For the purpose of this study, data from self-report questionnaires completed at 12 weeks gestation in the 'About Yourself' questionnaire, and at 18 weeks gestation in the 'Having a Baby' questionnaire were investigated.

Fertility

At 12 weeks women were asked if they had ever seen a doctor for infertility problems and if they had received treatment or help to conceive the current pregnancy, and were given the option to reply yes/no. Additionally, at 18 weeks gestation, women were asked about the duration of time it took them to conceive. Women were asked to indicate how long it took them to conceive from four possible options: less than 6 months, 6-11 months, 1-3 years and more than 3 years. Responses to this question were deemed to be non-applicable if the participants' pregnancy was unintentional; therefore the analyses for time taken to conceive was restricted to women who an intentional pregnancy (n=7,694). For the purpose of this study these options were collapsed into two dichotomous variables: less/more than 12 months (to investigate rates of infertility) and less/more than six months (to investigate underlying difficulties conceiving).

Intentional pregnancies

At 18 weeks gestation, women were asked if their current pregnancy was intentional and given the option to reply yes/no.

Reactions to pregnancy

At 18 weeks gestation all participants were asked how they felt when they discovered that they were pregnant and how they currently felt about their pregnancy. Responses were scored as: overjoyed/pleased, mixed feelings and not happy/very unhappy. In addition, at 12 weeks gestation participants were asked if becoming a mother meant giving up something important to them, responses were scored: yes a great deal/quite a lot and not really/definitely not.

Socio-demographic data

Socio-demographic factors (pre-pregnancy smoking, maternal age, occupation and marital status) known to affect the outcome variables were tested in all models as confounding variables. These variables were obtained via maternal self-report during pregnancy, a full description of the socio-demographic factors included in this investigation and how the data were handled is outlined Chapter 2, section 2.4.3. Increasing paternal age has also been shown to delay conception in the ALSPAC sample (Ford, et al., 2000), and was therefore included as a confounding variable within the analysis of conception time investigated in this chapter. At 18 weeks gestation a questionnaire was sent to the partner of the pregnant mother, which enquired about his age. Where paternal age is included as a confounder in the analysis, the questionnaire was completed by the biological father of the study child.

3.3.3 Statistical analysis

Cross-sectional analyses were carried out to determine the characteristics of the main outcome variables: time taken to conceive, frequencies of planned pregnancies, fertility related problems and treatment in groups of women reporting: AN, BN, AN+BN and compared to women in the unexposed group.

Univariate and multivariate logistic regressions were used to examine predictors of these main outcomes. Women's reactions to discovering their pregnancy and their current feelings towards their pregnancy were analysed using ordinal logistic

regressions. Potential covariates (maternal and paternal age, pre-pregnancy smoking, maternal education level and parity) that were likely to influence fertility and attitudes to pregnancy were included: 1. following a literature review of shown associations with the outcomes under study and 2. if they were associated with the predictor and outcome and not on the causal pathway. All analyses were performed using Stata (Version 10 for Windows) (StataCorp, 2009) and all statistical tests presented are two-tailed. Statistical significance was defined as a p value of less than 0.05.

Missing data

There was no selective attrition across the groups and missing data in the index groups on this variable were comparable to the unexposed group. Data on the age of the biological father was only available for 7,136 participants. An initial stratified analyses by parity suggested no differences in relation to the outcome across groups. Furthermore, a sensitivity analysis was carried out in relation to paternal age and there was no evidence that the association between exposure and outcome changed if data on paternal age was missing. Therefore, it was decided not to impute data on fathers' age.

3.4 Results

3.4.1 Socio-demographic data

Table 3.1 illustrates the socio-demographic data across the four groups. Maternal age at delivery, parity, employment and ethnicity did not differ across groups. Women with AN, BN and AN+BN were all more likely not to have a current partner compared to the unexposed group. Paternal age (biological father) was higher in women with AN+BN than in the unexposed group of women. Additionally women reporting AN and AN+BN were more likely to have smoked pre-pregnancy than women in the unexposed group.

Table 3.1: Socio-demographic data of participants included in analysis of time taken to conceive, by maternal eating disorder group

	AN **n=171**	**BN** **n=199**	**AN+BN** **n=82**	**Unexposed Group** **n=10, 636**
Maternal age at delivery: *mean (s.d.)*	*28.9 (5.2)*	*28.2 (4.6)*	*29.2 (4.6)*	*28.2 (4.8)* *p=0.062*
Maternal Education [1]:	48.7	40.8	56.2	36.6
(OR, 95% CI; *p value*)	(1.6, 1.1/2.2; *p*=0.002)	(1.7, 0.8/1.5; *p*=0.23)	(2.2 , 1.4/3.4; *p*<0.001)	Ref
Multiparity: %	52.5	51.6	53.3	54.9
(OR, 95% CI; *p* value)	(0.6, 0.6/1.2; *p*=0.52)	(0.9, 0.7/1.2; *p*=0.35)	(0.9, 0.6/1.5; *p*=0.76)	Ref
Pre-pregnancy Smoking: %	39.8	35.7	44.4	29.4
(OR, 95% CI; *p value*)	1.4 (1.0/2.0, *p*=0.05)	1.3 (0.9/1.8, *p*=0.10)	1.9 (1.2/2.9, *p*<0.001)	Ref
Fathers' Age: *mean (s.d.)*	*30.9 (6.2)*	*30.75 (5.8)*	*33.6* (6.2)*	*31 (5.2)* *p=0.009*

Comparisons based on ANOVA (in italics) and binary logistic regression; Ref = unexposed reference group

[1] full-time or part-time employment or full-time education, training vs. unemployed, housewives or retired at enrolment; [2] A-level/degree vs. CSE/None, Vocational, O-levels

3.4.2 Fertility

The majority of women across the four groups had never seen a doctor for fertility related problems (n=9,685, 88.1%), or used treatment or help with conceiving their current pregnancy (n=10,693, 97.3%). After adjusting for relevant confounders (maternal age, maternal education level, parity and pre-pregnancy smoking), women with AN (OR=1.6, 95% CI = 1.1/2.5; p=0.02) and women with AN+BN (OR=1.9, 95% CI = 1.1/3.4; p=0.02) were more likely to have seen by a doctor for fertility problems in their lifetime, compared to unexposed women. Furthermore, women with AN+BN were more than twice as likely (6.2%) as the unexposed group (2.7%) to have received treatment or help to conceive their current pregnancy (p=0.05). See Table 3.2.

3.4.3 Intentional pregnancy

Overall women in this sample were more likely to report that their current pregnancy was intentional (n=7,694; 71.4%). Women with lifetime AN were less likely to have unintentional pregnancies (41.5% vs. 28.3%), compared to the unexposed group (OR=0.5, 95% CI=0.4/0.7; p<0.001). This difference persisted when relevant confounders were entered into the model, see Table 3.2.

3.4.4 Time taken to conceive

Of the 7,694 women reporting a planned pregnancy, the majority conceived within the first six months (74.5%), with relatively few taking longer than 1 year (8.3%) or more than 3 years (3.6%) to conceive.

Two separate regression analyses were carried out primarily to investigate if there were any group differences for women having a duration of longer than 12 months to conceive (to investigate infertility) and secondly, for a duration of longer than 6 months (to investigate underlying fertility problems). The results of these analyses are shown in Table 3.3.

Overall women in the ED groups were no more likely to take longer than 12 months to conceive than unexposed women, in both univariate and adjusted analyses. However, there was some evidence that women reporting lifetime AN+BN took longer than 6 months to conceive, compared to the unexposed group; this difference persisted after the model was adjusted for relevant confounders (maternal age at delivery, maternal

education level, parity and pre-pregnancy smoking, paternal age; OR=1.9, 95% CI=1.0/3.5; p=0.03), see Table 3.3. In order to investigate the potential mediating role of maternal BMI on taking longer than 6 months to conceive a final model, incorporating pre-pregnancy BMI was tested. After including pre-pregnancy BMI in the model the results remained similar and women with AN+BN (OR=0.6, 95% = 0.2/0.9, p=0.032) continued to be more likely to take longer than six months to conceive, compared to the unexposed group.

Table 3.2: Logistic regression of fertility problems, intentional pregnancy and motherhood means personal sacrifice by maternal eating disorder group

	Unadjusted OR (95% CI)				Adjusted OR (95% CI) [1]		
	AN **n=171**	**BN** **n=199**	**AN+BN** **n=82**	**Unexposed Group** **n=10, 636**	**AN** **n=171**	**BN** **n=199**	**AN+BN** **n=82**
Seen a Dr. for Fertility Problems: n(%)	35 (20.6%)	22 (11.2%)	16 (19.5%)	1231 (11.7%)			
OR (95% CI, *p* value)	1.9 (1.3/2.8, *p*<0.001)	0.9 (0.6/1.49, *p*=0.84)	1.8 (1.1/3.1, *p*=0.03)	Ref	1.6 (1.1/2.5, *p*=0.02)	1.0 (0.6/1.6, *p*=0.99)	1.9 (1.1/3.4, *p*=0.02)
Received Help to Conceive: n(%)	4 (2.3%)	3 (1.5%)	5 (6.2%)	287 (2.7%)			
OR (95% CI, *p* value)	0.8(0.3/2.3, *p*=0.78)	0.5 (0.2/1.8, *p*=0.32)	2.3 (0.9/5.8, *p*=0.06)	Ref	0.8 (0.3/2.3, *p*=0.77)	0.6 (0.2/1.9, *p*=0.37)	2.4 (0.9/6.3, *p*=0.054)
Intentional Pregnancy: n(%)	96 (58.5%)	131 (67.1%)	53 (66.2%)	7,414 (71.7%)			
OR (95% CI, *p* value)	0.5 (0.4/0.8, *p*<0.001)	0.8 (0.6/1.0, *p*=0.16)	0.7 (0.5/1.2, *p*=0.27)	Ref	0.5 (0.4/0.7, *p*<0.001)	0.8 (0.6/1.0, *p*=0.12)	0.7 (0.4/1.1, *p*=0.18)

Odds Ratios (OR) with 95% Confidence Intervals (CI); Ref = unexposed reference group

[1] Adjusted for maternal age at delivery, parity, maternal educational level and pre-pregnancy smoking

Table 3.3: Logistic regression models of conception time by maternal eating disorder group

Time Taken To Conceive	**Unadjusted OR (95% CI)**				**Adjusted OR (95% CI)** [1]		
	AN **n=96**	**BN** **n=131**	**AN+BN** **n=53**	**Unexposed Group** **n=7,414**	**AN** **n=97**	**BN** **n=103**	**AN+BN** **n=54**
Model 1							
Failing to conceive within 12 months: *n (%)*	*14 (13.4)*	*11 (8.3)*	*8 (15.0)*	*781 (10.5)*			
OR (95% CI, *p* value)	1.3 (0.8/2.4, *p*=0.22)	0.9 (0.5/1.6, *p*=0.69)	1.5 (0.7/3.1, *p*=0.12)	Ref	1.0 (0.5/2.6, *p*=0.91)	0.7 (0.4/1.4, *p*=0.38)	1.5 (0.7/3.4, *p*=0.27)
Model 2							
Failing to conceive within 6 months *n (%)*	*23 (22.0)*	*21 (20.3)*	*19 (35.8)*	*1,730 (23.3)*			
OR (95% CI, *p* value)	1.0 (0.6/1.6, *p*=0.93)	0.6 (0.4/1.1, *p*=0.10)	1.7 (0.9/3.1, *p*=0.05)	Ref	0.9 (0.5/1.5, *p*=0.68)	0.6 (0.4/1.1, *p*=0.09)	1.9 (1.0/3.5, *p*=0.03)

Odds Ratios with 95% Confidence Intervals (CI); Ref =unexposed reference

[1] Adjusted for maternal age at delivery, parity, maternal educational level and pre-pregnancy smoking and partners' age

3.4.5 Feelings towards pregnancy

The majority of women in the ALSPAC sample reported feeling overjoyed/pleased when they discovered that they were pregnant (n=7,657, 71%), with few reporting negative feelings (not happy/very unhappy n=426, 3.9%).

Maternal ED was associated with a tendency to have negative feelings about the pregnancy. Women in the three ED groups showed increased odds of reporting negative feelings about discovering their pregnancy, compared to the unexposed group (seeTable 3.4). Women in the AN group had a 1.8 increase in odds of going up one category from being happy to unhappy, compared to unexposed women (adjusted OR=1.8, 95% CI=1.3/2.6, p<0.001).

At 18 weeks gestation negative feelings about pregnancy had reduced slightly in women with AN; however, there was a trend towards women with ED to continue to experience more negative feelings about their pregnancy than unexposed women. Furthermore, in the AN+BN group the odds of negative feelings towards pregnancy at 18 weeks gestation was 2.3 compared to the unexposed group (OR=2.3, 95% CI=1.3/4.1; p=0.03) (see Table 3.4).

At 12 weeks gestation relatively few women felt that motherhood meant giving up something important (n=1,181, 16.9%). However, women with AN (OR= 2.3, 95% CI=1.5/3.7, p<0.001) and AN+BN (OR= 2.4, 95% CI=1.3/2.6, p=0.004) were more likely to view motherhood as a personal sacrifice, compared to women in the unexposed group (see Table 3.4). After adjusting for confounding variable this difference remained in women with AN (OR= 1.7, 95% CI=1.2/2.5, p<0.002)

Table 3.4: Ordinal logistic regressions of participants' reaction pregnancy and logistic regression of motherhood means personal sacrifice by maternal group

	Unadjusted OR (95% CI)				**Adjusted OR(95% CI)[1]**		
Group	AN	BN	AN+BN	Unexposed Group	AN	BN	AN+BN
	n=171	n=199	n=82	n=10, 636	n=171	n=199	n=82
Feelings Upon Discovering Pregnancy:							
OR (95% CI, *p* value)	1.7 (1.3/2.4, *p*<0.001)	1.5 (1.1/2.1, *p*=0.003)	1.4 (0.5/2.2, *p*=0.15)	Ref	1.8 (1.3/2.6, p<0.001)	1.5 (1.2/2.1, p=0.003)	1.6 (1.0/2.6, p=0.042)
Feelings Towards Pregnancy at 18 weeks Gestation							
OR (95% CI, *p* value)	1.4 (0.9/2.2, *p*=0.12)	1.4 (0.9/2.1, *p*=0.07)	2.2 (1.3/3.9, *p*=0.003)	Ref	1.5 (0.9/2.4, p=0.59)	1.4 (0.9/2.2, p=0.091)	2.3 (1.3/4.1, p=0.003)
Motherhood Means Sacrifice:							
n(%)	47 (29.2%)	43 (22.5%)	23 (29.8%)	1,785 (17.7%)			
OR (95% CI, *p* value)	2.3 (1.5/3.7, *p*<0.001)	0.8 (0.5/1.4, *p*=0.23)	2.4 (1.3/4.6, *p*=0.004)	Ref	1.7 (1.2/2.5, p=0.002)	1.3 (0.9/1.9, p=0.11)	1.6 (0.9/2.8, p=0.49)

Odds Ratio (OR) with 95% Confidence Intervals (CI); Ref = unexposed reference [1] Adjusted for maternal age at delivery, parity and maternal educational level

3.5 Discussion

The aim of the current study was to investigate fertility, unplanned pregnancies and reactions to pregnancy in women with lifetime ED in large general population birth cohort.

3.5.1 Fertility

As hypothesised, women with ED, particularly women with a lifetime history of AN, were more likely to seek help to conceive and to take longer to conceive than women without ED. Specifically, women with lifetime AN (AN and AN+BN) were more likely to have been seen by a doctor for fertility problems prior to their current pregnancy than the unexposed group. Although only a small percentage of women had received treatment when trying to conceive across this sample, women with AN and BN were more than twice as likely to have received treatment for a fertility problem, compared to women without ED. This is the first study to investigate the prevalence of fertility treatment in women with ED from a large general population cohort, and corroborates previous research which has indicated that ED are common in women receiving fertility treatment, and that the prevalence of pregnancy may be reduced in women with ED (Brinch, et al., 1988; Freizinger, et al., 2008; Stewart, et al., 1990).

The underlying mechanisms resulting in fertility problems are complex and multifaceted, and both physiological and psychological factors are likely to contribute. However, it is important to note that the data from the present study relates to the early 1990s, since this time there have been a number of advances in the treatment of fertility problems, therefore different findings may be apparent if more recent data was available. Nevertheless, fertility treatment of the problems commonly seen in women with ED, such as hypogonadotrpic hypogonadism, has been widely available since the early 1990s.

Furthermore, the results of this investigation suggest that women with ED were no more likely than unexposed women group to take longer than 12 months to conceive. However, after adjusting for relevant maternal and paternal covariates, women reporting a history of both AN and BN were more likely to take longer than six months to conceive their current pregnancy. Furthermore, after including pre-pregnancy BMI in the analysis women with a history of both AN and BN continued to be more likely to take longer to conceive, compared to women without ED.

This finding, in combination with the findings above suggest that although infertility was uncommon in this sample, underlying fertility related problems and difficulties conceiving existed, particularly in women with a history of both AN and BN. It is of note that this group of women had the highest prevalence of lifetime purging and lowest pre-conception BMI across the three index groups (Micali, Simonoff, et al., 2007b), see section 2.4.5 of the General Aims and Methodology Chapter for full details of lifetime ED behaviours in these groups. Severity of the ED might therefore explain the higher risk for fertility related problems in this group; as they appear to be at greatest risk of experiencing both fertility problems and delays in conceiving.

These findings are consistent with previous long-term follow up studies, which suggest that in general, fertility is affected but not significantly compromised in women with ED (Bulik, et al., 1999; Crow, et al., 2002). However, the women in this study were pregnant at the time of enrolment, hence were able to conceive, therefore they might be representative of a less severe group of women with ED, which may result in an underestimation, rather than overestimation of fertility related problems in this group.

Unintentional pregnancies

As hypothesised, women with ED, specifically those with lifetime AN were more likely to an unplanned pregnancy compared to women without ED. Specifically, approximately 40% of women with AN reported that their current pregnancy was unintentional. These findings are consistent with findings from the MoBa study, which indicated that more than half of pregnancies in their sample of women with AN were unplanned (Bulik, et al., 2010). Women with AN often experience amenorrhea or oligomenorrhea, which may persist even after recovery from the disorder (Golden, et al., 1997); however ovulation and pregnancy could still occur in women with ED who experience irregular cycles (Andersen & Ryan, 2009). It is possible that the high number of unplanned pregnancies found in this investigation may result from erroneous beliefs about their ability to become pregnant, and therefore lack of contraceptive use.

3.5.2 Reactions to pregnancy

Across all three ED groups, negative feelings towards discovering that they were pregnant were more frequent than in women without ED. For women with a history of both AN and BN negative feelings remained frequent at18 weeks gestation but had reduced in women in either the AN or BN groups. In general, ED symptoms have been shown to reduce during pregnancy (Lacey & Smith, 1987; Lemberg & Phillips, 1989;

Micali, Treasure, et al., 2007b; Morgan, et al., 1999c), and it has been suggested that maternal concern for their unborn child may override ED behaviours. This may help explain the adjustments in feelings towards pregnancy later in pregnancy in the AN and BN groups.

Furthermore, women with lifetime AN more frequently viewed motherhood as a personal sacrifice. Women suffering with AN often highly value aspects of their illness, and perceive the AN as providing several benefits. Since pregnancy inevitably involves weight gain, becoming a mother may be seen as threatening to a potentially valued "anorexic identity" (Schmidt & Treasure, 2006). Negative feelings in the ED group possibly result from a combination of the unexpected discovery of pregnancy combined with the prospect of weight gain during pregnancy. The pre-natal period has been shown to be an important time for maternal bonding, and has been found to reflect attachment once the baby is born (Gipson, et al., 2008; Stone & Menken, 2008). Women with ED have also been found to have difficulties adjusting to motherhood, therefore the pre-partum period may be a risk factor for difficulties with attachment in the post-natal period, and therefore an important time for interventions aimed at improving pre-natal bonding and adjustment to becoming a mother once the baby is born.

3.5.3 Strengths and limitations

This study is the first study to systematically investigate conception time in women with lifetime ED from a general population cohort and additionally to distinguish between different ED classifications. Furthermore, the availability of data on important confounders allowed a less biased investigation of relevant outcomes in women with ED. Investigating the time taken to conceive is thought to be a more sensitive measure of fertility problems in epidemiological samples, compared to research outcomes previously utilised in this field.

There are some limitations to this study, which require consideration when interpreting the results. This study is subject to the general limitations pertaining to the use of ALSPAC, discussed in section 2.4.5 (ALSPAC: general methodological considerations). In addition, it is also important to note that, given the nature of the sampling procedure, all women within this study were able to become pregnant, women in the ED groups might be representative of a less severe ED sample, compared to a

clinical sample. However, should this be true, this is likely to cause an underestimation of fertility problems across ED groups.

3.5.4 Conclusions and clinical Implications

The present study has important implications for the treatment of women with ED, during their childbearing years. Underlying difficulties conceiving were indicated by a higher percentage of women in the AN and BN group taking longer than six months to conceive and seeking advice or help for a fertility related problem. The current NICE guidelines on fertility treatment recommend that "women should be informed that female BMI should ideally be in the range 19–30 before commencing assisted reproduction, and that a female body mass index outside this range is likely to reduce the success of assisted reproduction procedures" (National Institute for Clinical Excellence, 2004); however, no specific guidelines are currently available on fertility treatment in women with ED. Given the obstetric risks associated with ED (Brinch, et al., 1988; Bulik, et al., 1999; Micali, Simonoff, et al., 2007a; Morgan, et al., 2006; Sollid, et al., 2004; Stewart, et al., 1987), NICE guidelines should be extended to highlight the need for psychological treatment for women with ED, and a reduction in ED symptoms, prior to assisted reproduction treatment.

Furthermore, given that many women do not disclose their ED history to obstetricians (Freizinger, et al., 2008), the findings from this investigation further emphasise the importance for health care professionals to routinely screen women who are experiencing difficulties conceiving for ED, in order to provide appropriate help and advice.

Moreover, unplanned pregnancies were found to be more common in this sample, confirming recent findings from women with AN in a separate large birth cohort (MoBa; Bulik, et al., 2010). These findings might underlie an underestimation of the chances of conceiving in women with AN. ED specialists are ideally placed to approach issues of fertility and family planning with their patients early on during treatment. To overcome possible mistaken beliefs about fertility, women with ED should be informed by their clinicians that they can be fertile, even when experiencing disturbed menstrual patterns. In addition, given that many women with ED fail to discuss their illness with midwifes and obstetricians, multidisciplinary working and the formation of close links with obstetric and gynaecological services should be encouraged when working with a patient who is pregnant.

Negative feelings towards becoming pregnant were more frequent within the ED groups, particularly on finding out about pregnancy. Therefore the early phases of pregnancy may be particularly difficult for women with ED and additional support should be given in this period in order to assist transition to motherhood.

Chapter 4. Dietary Patterns and Macronutrient Intake in Children of Mothers with Eating Disorders: A Longitudinal Investigation

Parts of the chapter have been submitted as a regular article to Journal of Pediatrics and the findings were presented at the Academy of Eating Disorders 2010 International Conference of Eating Disorders [8,9]

4.1 Introduction

Given that ED are typically characterised by severely disrupted eating habits and preoccupations with body weight and shape, mothers with ED may find catering for the nutritional needs of their children especially challenging. However, few studies have investigated the impact of a maternal ED on their child's diet. The scarce literature highlighted in Chapter 1, section 1.11 indicates that maternal feeding practices may be difficult for women with ED, and that the risk for feeding difficulties is elevated in their children (Micali, et al., 2009; Park, et al., 2003; Patel, et al., 2002). High levels of conflict during mealtimes have also been reported in family's where the mother has experienced an ED (Stein, Woolley, & McPherson, 1999). Furthermore, mothers with ED tend to hold more distorted perceptions of their child's weight and shape (Agras, et al., 1999), cook less regularly for their children (Woodside & Shekter Wolfson, 1990) and fear that preparing food for their children may lead to episodes of bingeing (Fahy & Treasure, 1989; Lacey & Smith, 1987). These difficulties may lead to differential dietary patterns and nutritional intake in their children, which may have long-term implications for their health and development of dietary preferences during adolescence.

Only one previous study has investigated the dietary intake in children whose mothers have an ED (Waugh & Bulik, 1999); although this study found the diet of children of women with ED to be generally unaffected, there was some suggestion that children of

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[8] Easter, A., Naumann, U., Northstone, K., Schmidt, U., Treasure, J., & Micali, N. (Submitted). A longitudinal investigation of dietary patterns and nutritional intake in children of mothers with Eating Disorders.

[9] I presented the findings of this investigation at the Academy of Eating Disorders (AED) 2010 International Conference of Eating Disorders, for which I received an AED Early Careers Investigator Fellowship

women with ED consumed less junk food than children in the control group. However, this particular study was limited by small sample size, and was drawn from a sample of children at different ages at a single time point. No previous studies have longitudinally investigated dietary patterns and nutritional intake in children of women with ED.

4.2 Aims and hypotheses

The purpose of this study was to explore different dietary patterns and macronutrient intake in children of women with ED, compared to children of women without ED, in a longitudinal fashion, using a large prospective population-based cohort. Specifically this study aimed to investigate:

1. adherence to dietary patterns in children of mothers with ED, compared to children of women without a history of ED, from three to nine years;
2. differences in macronutrient consumption in children of women with ED, compared to children of women without a history of ED, from three to nine years;
3. the effect of ED sub-type and child gender on dietary patterns and macronutrient consumption in the children of mothers with ED, compared to women without a history of ED.

Hypothesis under investigation

1. Children of women with AN will show greater adherence to a 'health conscious' dietary pattern, compared to children of women without a history of ED.
2. Children of women with BN will show greater adherence to 'snack' and 'processed' dietary patterns, compared to children of women without a history of ED.
3. Children of women with AN will have reduced energy and macronutrient intake, compared to children of women without a history of ED.
4. Children of women with BN will have increased energy and macronutrient intake, compared to children of women without a history of ED.

4.3 Methods

4.3.1 Design and participants

This study is based on data collected as part of ALSPAC (Golding, et al., 2001), full details of the ALSPAC study are described in General Aims and Methodology Chapter (Section 2.4).

For the purpose of this study only included singleton births were included (n=12,254), and women who reported having a psychiatric disorder other than an ED were excluded (n=1,166). As described previously (section 2.4.4) women were divided according to self-reported ED classification: AN n=171 (1.5%), BN n=199 (1.8%), and AN+BN n=82 (0.7%) responded yes to both having ever had AN and BN (AN+BN), the remaining 10,636 (96%) reported no prior history of an ED (and formed the unexposed comparison group).

4.3.2 Outcomes and measures

Socio-demographic data

Maternal socio-demographic factors (maternal age at delivery, ethnicity, parity, household income) and child gender, which have previously associated with childhood diet and known to affect the outcome variables, were included in the models as confounding variables in the analyses. Maternal socio-demographic were obtained via maternal self-report during pregnancy, child gender was obtained at birth. A full description of these variables and how the data were handled is outlined in Chapter 2.

Food Frequency Questionnaire

The present study uses data collected from Food Frequency Questionnaires (FFQ) completed by the study child's mother when the children were 38, 54, 81 and 103 months of age. For ease of reporting and interpretation these time points will be referred to by the child's approximate age in years throughout this chapter; 3, 4, 7 and 9, respectively. Each FFQ contained a set of questions enquiring about the frequency of consumption of a wide range of foods and drinks. The mother, or main carer, was asked to indicate how often her child was currently consuming a variety of food items: 'never or rarely' (1) 'once in 2 weeks' (2) 'one to three times per week' (3) 'four to seven times per week' (4) more than once per day (5).

In order to interpret FFQ data, assessment of dietary patterns, as opposed to individual food items, is a widely used method of investigating food consumption in nutritional epidemiology. Principle component analysis (PCA) is one way of deriving dietary patterns of similar food groups from single food items derived from FFQ. This method allows an examination of the whole-diet of the children and accounts for the relationship between individual food items. Therefore, for the purpose of this thesis, predefined dietary patterns and macronutrient consumption derived from the FFQ are used to investigate differences between children of women with and without ED.

4.3.3 Procedures

Data preparation

Prior to the analysis conducted as part of this thesis, the data collected from the FFQ were numerically transformed into the number of times consumed per week (0. 0.5, 2, 5.5, 10 respectively). All data were standardised by subtracting the mean and dividing by the standard deviation for each variable; this was necessary because the consumption of tea, coffee, cola and bread were measured on a different scale to the other variables (North & Emmett, 2000; Northstone & Emmett, 2005; Northstone & Emmett, 2008).

Furthermore, prior to the investigation presented in this chapter PCA was carried out in order to extract dietary patterns and nutrition intake was calculated at each time point by Kate Northstone and Pauline Emmet (North & Emmett, 2000; Northstone & Emmett, 2005; Northstone & Emmett, 2008). Statistical methods of this data preparation, and the 'dietary patterns' identified, are summarised below (North & Emmett, 2000; Northstone & Emmett, 2005; Northstone & Emmett, 2008).

Dietary patterns

PCA with varimax rotation (Gorsuch, 1974; Kline, 1994) was performed on the standardised food items. Foods with loadings above 0.3 on a component were considered to have a strong association and were used to describe the dietary patterns. At each time point, dietary patterns were given a label to describe the underlying pattern and aid in the reporting and discussion of the results.

Three distinct dietary patterns were derived from the PCA: 1. 'processed', 2. 'health conscious', 3. 'traditional' at each time point. The 'processed' pattern was characterised by increased consumption of high-fat, processed foods (such as sausages, burgers and poultry products) and snack foods high in fat and/or sugar (such as crisps, sweets,

chocolate, ice lollies and ice creams). The 'traditional' pattern was associated with consumption of meat, poultry, potato and vegetable, typical of a British "meat and two veg" dinner. The third dietary pattern, 'health-conscious', was characterised by a diet high in vegetarian foods, nuts, salad, rice, pasta, fruit, cheese, fish, cereal, water and fruit juice. This pattern was slightly modified at 9 years of age, where meat products were negatively associated with this dietary pattern and the pattern was relabelled 'health conscious/vegetarian' (Northstone & Emmett, 2008).

An additional dietary pattern was identified at the age of three and was labelled "snack foods", which was described as a diet primarily consisting of snacks and finger foods, rather than meals where cooking is required, and loaded highly on fatty foods such as cakes, biscuits and crisps, but was also positively associated with frequent consumption of bread and fruit (North & Emmett, 2000).

For each child, a score was created for each dietary pattern identified at each time point by multiplying the factor loadings by the corresponding standardised value for each food and summing across the food items. This score is used in the analysis in the chapter (described below) in order to assess adherence to specific dietary patterns (whereby increasing scores implies greater adherence) over the four time points.

Nutritional data

Data from the FFQs were used to estimate nutrient intakes at each age. Macronutrient intake, of energy (kj), fat (g), carbohydrate (g), protein (g), starch (g) and sugar (g), was calculated by multiplying the weekly frequency of consumption of each type of food by its estimated nutrient content, and summing this across all foods consumed (Ong, et al., 2007).

Socio-demographic data: Socio-demographic factors (education, ethnicity, household income, parity and ethnicity) previously found to be associated with childhood diet were considered as confounding variables in the following analyses. These variables were obtained via maternal self-report during pregnancy; child gender was recorded at the time of birth. A full description of the socio-demographic factors included in this investigation and how the data were handled is outlined in Chapter 2.

Statistical analysis[10]

Univariate analysis of variance (ANOVA) and binary logistic regressions were used to assess differences in participant characteristics in groups of women reporting AN, BN and AN+BN, compared without an ED history (the unexposed group). The associations between each dietary pattern and predictors (described in detail below) were assessed using linear mixed-effects models, using the statistical software, Stata (version 10) (StataCorp, 2009).

Longitudinal data analysis

Analysis of dietary patterns: Longitudinal data were available at all four time points for three dietary patterns as described above: 'health conscious/vegetarian', 'traditional' and 'processed'. The associations between each dietary pattern score and predictors were assessed using linear mixed-effects models. These models are commonly used for modelling longitudinal data (Singer & Willett, 2003). The predictor variables were maternal group and the time point at which dietary patterns were assessed in the children. The mean time of completion at assessment was included as a continuous variable. A random intercept for individuals was included in the model to take account of the variance in the data that is due to individual differences.

Since the dietary pattern 'snacks' was only identified in the three year old children, a linear regression model was used to assess group differences in this pattern score.

Missing data

Due to missing data on longitudinal dietary patterns a dataset derived from multiple imputations was used for these analyses. Switching regression (Van Buuren, Boshuizen, & Knook, 1999), which is an iterative multivariable regression technique for handling missing data, was used to impute plausible values for the missing data. This procedure generated separate copies of the original data set with values imputed from the switching regression analysis. Five imputations were used in the present investigation to produce datasets without missing values. Estimates were then combined and averaged across the five datasets, according to the rules of Rubin (Rubin, 1987) in order to obtain valid overall estimates. For the outcomes, the fraction of missing observations, which

[10] The statistical procedures undertaken in this chapter were carried out in collaboration with Ulrike Naumann, Statistician at the Institute of Psychiatry, Kings College London.

were then recovered by the multiple imputation, were 8.8%, 13.2%, 23.8% and 29.4%, for the dietary patterns at 3, 4, 7 and 9 respectively. This data set resulted in dietary patterns and macronutrient data on 9,423 children, 140 mothers with a history of AN, 175 a history of BN and 9,037 reported no prior history of psychiatric illness.

Analysis of nutrients: Longitudinal nutrient intake across ED groups was also investigated using linear mixed-effects models (using maternal ED as the predictor), and random intercepts. In order to correct skewed data, all nutrient data were log-transformed to normal distribution prior to analysis.

The models were run unadjusted initially and then adjusted for potential covariates previously found to be associated with relevant outcomes in this sample and likely to influence outcomes: maternal age, education, ethnicity, household income, parity, and child gender (Northstone & Emmett, 2008). In order to investigating the role of child gender and age on the main outcome variables group-by-time point and group-by-child gender interaction terms were tested in all models.

4.4 Results

4.4.1 Socio-demographic data

Women included in the study were compared according to ED group on several socioeconomic variables (see Table 4.1). Maternal age at delivery, ethnicity, parity, household income and child gender did not differ across the four groups. Mothers with AN (OR=1.6, 95% CI= 1.1/2.2, p=0.005) and AN+BN (OR=2.2, 95% CI= 1.4/3.5, p<0.001) were more likely to be educated to A-level or degree level than the unexposed group.

4.4.2 Dietary *patterns*

'Snack' dietary pattern

Linear regression of the 'snack' dietary pattern indicated that consumption of 'snacks' at 3 years was similar in the children of women with ED (Table 4.2). After adjusting for confounding variables there were no differences between children in the maternal ED groups and the unexposed group: AN: adjusted coefficient = -0.22, 95% CI -0.22/0.13, p=0.61; BN: adjusted coefficient = -0.1, 95% CI = -0.14/0.16, p=0.92; AN+BN: adjusted coefficient = 0.9, 95% CI= -0.14/-0.32.

Table 4.1: Maternal and child socio-demographic data for children included in dietary patterns and macronutrient models by maternal groups

	AN n=140	BN n=175	AN+BN n=71	Unexposed Group n=9,037
Age at delivery: *mean (s.d.)*	*29.2 (5.4)*	*28.4 (4.4)*	*29.2 (4.6)*	*28.5 (4.6)* *p=0.053*
Maternal Education:	50.7	39.8	57.7	38.6
% A-level/degree	(1.6, 1.2/2.3; p=0.005)	(1.1, 0.77/1.4; p=0.74)	(2.2 , 1.4/3.5; p<0.001)	*REF*
(OR, 95% CI; p value)				
White Ethnicity: %	96.3	97.6	100	97.6
(OR, 95% CI; p value)	(0.5, 0.21/1.3; p=0.73)	(0.8, 0.31/1.3; p=0.73)		*REF*
Multiparity: %	52.2	49.1	51.5	54.6
(OR, 95% CI; p value)	(0.9, 0.61/1.3; p=0.58)	(0.8, 0.59/1.2; p=0.35)	(0.9, 0.55/1.4; p=0.60)	*REF*
Child Gender: % female	48.5	50.2	48.8	48.8
(OR, 95% CI; p value)	(0.9, 0.68/1.3; p=79)	(1.1, 0.83/1.5; p=0.51)	(0.9, 0.61/1.5; p=0.90)	*REF*

Based on ANOVA (in italics) and binary logistic regression (*REF*= unexposed reference group)

Table 4.2: Linear regression of "snack" dietary pattern at 3 years by maternal group eating disorder group

	Coefficient	95% CI		p value
		Lower	Upper	
Unadjusted Model				
AN (n = 140)	-0.08	-0.25	0.09	0.35
BN (n = 175)	-0.02	-0.17	0.13	0.79
AN+BN (n = 71)	-0.12	-0.11	0.36	0.31
Adjusted Model[1]				
AN (n = 140)	-0.05	-0.22	0.13	0.61
BN (n = 175)	0.01	-0.14	0.16	0.92
AN+BN (n = 71)	0.09	-0.14	-0.32	0.44

compared to children of women without ED (unexposed reference group; n=9,073)

[1] adjusted for: maternal age, education, ethnicity, household income, parity and child gender

'Health Conscious' dietary pattern

Table 4.3 summarises the results of adherence to specific dietary patterns over the four time points, across maternal exposure groups, for the: 'traditional', 'health conscious' and 'processed' dietary pattern.

Children of mothers with a history of an ED had higher scores on the 'health conscious' dietary pattern across the four time-points, compared to children in the unexposed group: AN (coefficient = 0.29, 95% CI = 0.15/0.43, p<0.001) BN (coefficient = 0.32, 95% CI = 0.19/0.45, p<0.001) and AN+BN (coefficient = 0.43, 95% CI = 0.24/0.63, p<0.001). After adjusting for confounding variables (maternal age, education, ethnicity, household income, parity and child gender) these differences persisted in the maternal AN (adjusted coefficient = 0.35, 95% CI = 0.16/0.54, p<0.001) and maternal BN (adjusted coefficient = 0.20, 95% CI = 0.04/0.37, p=0.014) groups, compared to the unexposed group. See Table 4.3

There was a group by gender interaction on the 'health conscious' dietary pattern: male children of women in the AN group were less likely to adhere to this pattern than females (adjusted coefficient = -0.29, 95% CI = -0.55/-0.03, p=0.025); conversely male children of mothers reporting both AN+BN were more likely to have higher scores on the health conscious pattern compared to female children (adjusted coefficient = 0.39, 95% CI = 0.03/0.76, p=0.03).

Table 4.3: Mixed effects models of childhood dietary patterns between 3 and 9 years by maternal eating disorder group

	Unadjusted Models				Adjusted Models[1]			
	Coefficient	95% CI		P value	Coefficient	95% CI		P value
		Lower	Upper			Lower	Upper	
'Health Conscious' dietary pattern 3-9 years								
AN (n = 140)	0.29	0.15	0.43	<0.001	0.35	0.16	.54	< 0.001
BN (n = 175)	0.32	0.19	0.45	<0.001	0.20	0.04	.37	0.01
AN+BN (n = 71)	0.43	0.24	0.63	<0.001	0.12	-0.13	.39	0.33
Time	*-0.003*	*0.086*	*-0.0001*	*0.063*	*-0.003*	*-0.006*	*.0002*	*0.07*
Gender X Group					*-0.051*	*-0.082*	*-0.01*	*0.002*
Male X AN					*-0.29*	*-0.55*	*-0.03*	*0.02*
Male X BN					*0.14*	*-0.09*	*0.39*	*0.23*
Male X AN+BN					*0.39*	*0.03*	*0.76*	*0.03*
'Processed' dietary pattern 3-9 years								
AN (n = 140)	-0.04	0.09	-0.18	0.53	0.01	-0.12	0.14	0.86
BN (n = 175)	-0.08	0.03	-0.21	0.16	-0.07	-0.19	0.04	0.22
AN+BN (n = 71)	-0.04	0.14	-0.24	0.63	0.05	-0.14	0.23	0.62
Time	*0.007*	*0.003*	*0.01*	*<0.001*	*0.01*	*0.018*	*0.005*	*<0.001*
'Traditional' dietary pattern 3-9 years								
AN (n = 140)	-0.21	-0.43	-0.01	0.05	-0.24	-0.46	-0.02	0.03
BN (n = 175)	-0.35	-0.45	0.15	<0.001	-0.37	-0.56	-0.18	< 0.001
AN+BN (n = 71)	-0.32	-0.63	-0.03	0.02	-0.28	-0.59	0.032	0.07
Time	-0.002	-0.006	0.001	0.14	*-0.005*	*-0.008*	*-0.001*	*0.009*
Time X AN	0.028	-0.003	0.06	0.08	*0.034*	*0.003*	*0.066*	*0.03*
Time X BN	0.044	0.015	0.073	0.003	*0.049*	*0.024*	*0.074*	*< 0.001*
Time X AN+BN	0.061	0.019	0.104	0.005	*0.048*	*0.003*	*0.092*	*0.033*

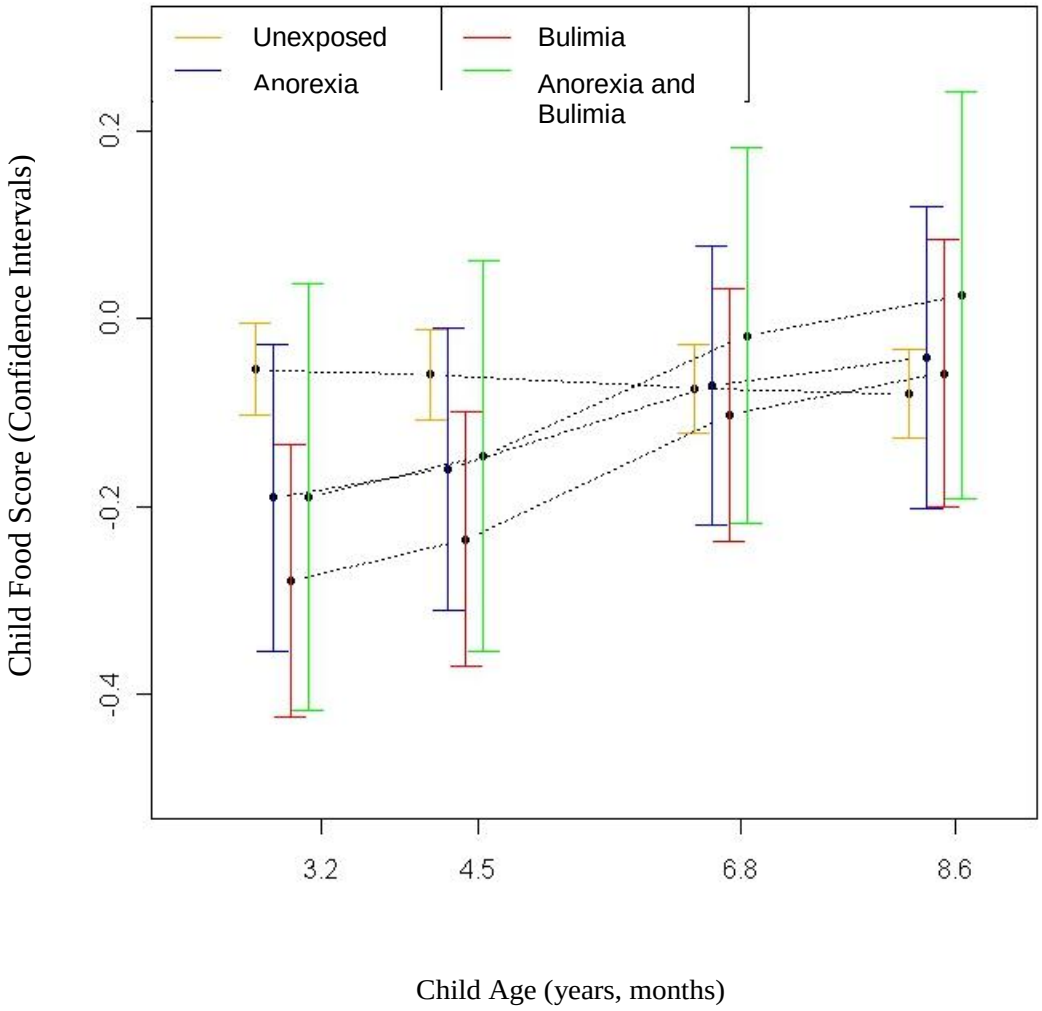
Unexposed general population group reference n=9037;

[1] adjusted for: maternal age, education, ethnicity, household income, parity and child gender

'Traditional' dietary pattern

Children in all exposed groups scored lower on the 'traditional' dietary pattern across the four time-points, compared to children in the unexposed group. After adjusting for covariates these differences persisted in the maternal AN (adjusted coefficient = -0.24, 95% CI = -0.46/-0.02, p=0.03) and maternal BN (adjusted coefficient = -0.37, 95% CI = -0.56/-0.18, p<0.001) groups, and a trend remained in the maternal AN+BN (coefficient = -0.28, 95% CI = -0.59/0.03, p=0.07), compared to the unexposed group. There was a significant group by time-point interaction: with scores in all index groups increasing over time, in comparison to children in the unexposed group who had decreasing scores over childhood, see Figure 4.1.

Figure 4.1 Traditional mean dietary pattern score with 95% confidence intervals over childhood by maternal eating disorder group



'Processed' dietary pattern

Scores on the 'processed' dietary pattern were similar in the maternal ED groups, compared to children in the unexposed group, in both adjusted and unadjusted models, Table 4.3. In all groups, 'processed' food scores increased between the ages of 3 and 9 years (adjusted coefficient = 0.01, 95% CI = 0.01/0.005, p<0.001).

4.4.3 Nutrient content

Mixed effect models were used to assess consumption of nutrients (energy, fat, sugar, protein, starch and carbohydrates) across the four time points. Table 4.3 and Table 4.4display the results of these analyses.

Consumption of sugar, energy, fat, starch and protein was higher in children of women reporting both AN+BN, compared to children in the unexposed group. The pattern was similar in both unadjusted and models adjusted for maternal age, education, ethnicity, household income, parity and child gender (Table 4.3 and Table 4.4).

Conversely, in adjusted analysis children of women with BN consumed less sugar (log-transformed coefficient = -0.08, 95% CI = -0.16/-0.01, p=0.02), than children in the unexposed group. Furthermore, in adjusted analysis there were trends for children of women with BN to consume less energy (log-transformed coefficient = -0.05, 95% CI = -0.11/-0.004, p=0.06), protein (log-transformed coefficient = -0.04, 95% CI = -0.10/-0.02, p=0.18), and carbohydrate (log-transformed coefficient = -0.05, 95% CI = -0.12/0.01, p=0.08), compared to children in the unexposed group.

In all groups nutritional intake increased over childhood, see Table 4.3 and Table 4.4. In the maternal BN group energy, carbohydrate, starch and sugar intake increased significantly over time, compared to the unexposed group. Similarly, consumption of fat intake increased over time in the maternal AN+BN group, compared to the unexposed group.

Table 4.4: Mixed effects models of childhood log transformed energy, fat and protein intake between 3 and 9 years by maternal eating disorder group

	Unadjusted Models				Adjusted Models [1]			
Coefficient	Coefficient	95% CI		P value	Coefficient	95% CI		P value
		Lower	Upper			Lower	Upper	
Energy (kj) 3-9 years								
AN (n = 140)	-0.04	-0.10	-0.02	0.198	-0.02	-0.08	0.04	0.51
BN (n = 175)	-0.03	-0.09	0.01	0.16	-0.05	-0.11	0.004	0.06
AN+BN (n = 71)	0.08	0.004	0.16	0.03	0.08	-0.01	0.169	0.07
Time in years	*0.08*	*0.08*	*0.08*	*<0.001*	*0.085*	*0.08*	*0.09*	*<0.001*
Time X AN	*0.007*	*-0.001*	*0.01*	*0.11*	*0.006*	*-0.0043*	*0.01*	*0.25*
Time X BN	*0.007*	*-0.0007*	*0.01*	*0.071*	*0.009*	*0.0005*	*0.01*	*0.03*
Time X AN+BN	*-0.003*	*-0.015*	*0.008*	*0.56*	*-0.001*	*-0.01*	*0.01*	*0.81*
Fat (g) 3-9 years								
AN (n = 140)	-0.05	-0.11	0.01	0.13	0.01	-0.02	0.05	0.44
BN (n = 175)	-0.04	-0.10	0.02	0.17	-0.01	-0.04	0.02	0.60
AN+BN (n = 71)	0.06	-0.02	0.15	0.14	0.06	0.007	0.11	0.02
Time	*0.08*	*0.084*	*0.086*	*<0.00*	*0.08*	*0.08*	*0.09*	*<0.001*
Protein (g) 3-9 years								
AN (n = 140)	-0.001	-0.03	0.03	0.94	0.013	-0.05	0.08	0.71
BN (n = 175)	0.01	-0.02	0.04	0.50	-0.042	-0.10	0.02	0.18
AN+BN (n = 71)	0.06	0 .30	0.31	0.01	0.12	0.02	0.20	0.01
Time in years	*0.08*	*0.083*	*0.085*	*<0.001*	*0.08*	*0.08*	*0.09*	*<0.001*

[1]adjusted for: maternal age, education, ethnicity, household income, parity and child gender

Table 4.5: Mixed effects models of childhood log transformed carbohydrate, starch and sugar intake between 3 and 9 years by maternal eating disorder group

Coefficient	Unadjusted Models				Adjusted Models [1]			
	Coefficient	95% CI		P value	Coefficient	95% CI		P value
		Lower	Upper			Lower	Upper	
Carbohydrates (g) 3-9 years								
AN (n = 140)	-0.04	-0.11	0.02	0.20	-0.01	0.09	0.05	0.62
BN (n = 175)	-0.03	-0.09	0.02	0.23	-0.05	-0.12	0.01	0.08
AN+BN (n = 71)	-0.03	0.09	0.18	0.02	0.07	-0.02	0.16	0.14
Time in years	0.08	0.083	0.085	<0.001	*0.087*	*0.08*	*0.09*	*<0.001*
Time X AN	0.007	-0.002	0.01	0.158	*0.004*	*-0.006*	*0.01*	*0.39*
Time X BN	0.008	-0.0004	0.01	0.061	*0.01*	*0.001*	*0.02*	*0.03*
Time X AN+BN	-0.003	-0.01	0.009	0.609	*0.001*	*-0.01*	*0.01*	*0.85*
Starch (g) 3-9 years								
AN (n = 140)	-0.004	0.04	0.03	0.81	0.001	-0.04	0.04	0.95
BN (n = 175)	0.02	-0.009	0.06	0.14	0.01	-0.02	0.05	0.49
AN+BN (n = 71)	0.09	0.04	0.15	<0.001	0.08	0.03	0.14	0.003
Time in years	*0.095*	*0.093*	*0.09*	*<0.001*	*0.09*	*0.10*	*0.099*	*<0.001*
Sugar (g) 3-9 years								
AN (n = 140)	-0.04	-0.11	0.03	0.28	-.0017	-0.09	0.06	0.68
BN (n = 175)	-0.06	-0.13	0.002	0.061	-0.08	-0.16	-0.01	0.03
AN+BN (n = 71)	0.12	-0.02	0.22	0.018	0.11	0.0003	0.22	0.05
Time in years	*0.074*	*0.072*	*0.07*	*<0.001*	*0.077*	*0.075*	*0.07*	*<0.001*
Time X AN	*0.007*	*-0.003*	*0.018*	*0.19*	*0.006*	*-0.006*	*0.018*	*0.32*
Time X BN	*0.01*	*0.0004*	*0.02*	*0.042*	*0.014*	*0.002*	*0.025*	*0.015*
Time X AN+BN	*-0.012*	*-0.02*	*0.001*	*0.087*	*-0.008*	*-0.024*	*0.007*	*0.27*

[1] adjusted for: maternal age, education, ethnicity, household income, parity and child gender

4.5 Discussion

This study aimed to examine longitudinal patterns of food consumption in the children of mothers with ED compared to children whose mothers had no history of ED. Reassuringly no gross deficits were observed in the dietary intake of children whose mothers have an ED, nevertheless some important differences in their diet are highlighted.

4.5.1 Dietary patterns

Children born to mothers with ED were less likely to adhere to a "traditional" dietary pattern, than children of women without ED. This dietary pattern is synonymous with a British 'meat and two veg diet', which would typically be eaten at mealtimes. Family mealtimes have been shown to be particularly difficult for mothers who have experienced an ED, as such elevated levels of conflict during mealtimes have been reported (Stein, et al., 1999). Therefore, in line with previous research, reduced adherence to the 'traditional' dietary pattern in this study might reflect less frequent traditional mealtimes in families where the mother has an ED.

As hypothesised, children of mothers with ED showed greater adherence to a 'health conscious' dietary pattern, which is associated with foods such as salad, rice and fruit; and is consistent with a vegetarian diet in late childhood. It has previously been demonstrated that women with AN in this sample were more likely to follow this dietary pattern in pregnancy themselves (Micali, et al., in press) these findings might imply a stronger maternal desire in women with ED to provide a healthy diet for their children. Furthermore, although there were no differences in the adherence to 'processed' or 'snack' dietary patterns in this study, the finding of greater adherence to a 'health conscious' dietary pattern to is in line with suggestions from previous research, which indicated that children of women with ED may consume less junk foods (Waugh & Bulik, 1999)

It is currently not known what effects increased exposure to a 'health conscious/vegetarian' diet during childhood may have on later child health and development; however previous evidence from this sample suggests cross-sectional associations between adherence to this dietary pattern and positive developmental outcomes (Feinstein, et al., 2008; Northstone, Joinson, Emmett, Ness, & Paus). It will

be important to continue to investigate dietary preferences and attitudes during adolescence in this sample, in order to assess long-term outcomes.

4.5.2 Nutrient intake

Consistent with our finding of greater adherence to a health conscious dietary pattern in children of women with ED, there was some evidence that children of women with BN consumed less energy, protein and carbohydrates than children in the unexposed group. In contrast, children of women reporting a history of both AN and BN consumed a diet higher in several macronutrients. This finding was surprising given that adherence to the 'snacks' and 'processed' dietary pattern was similar in this group of children, and further replication in large samples is required. Greater consumption of high energy dense foods is associated with over-eating and bingeing, and may be a risk factor for greater weight gain and eating disturbances later in life in this group of children.

4.5.3 Changes in diet across childhood

Over time children of women with ED were consuming more 'traditional' and less 'health conscious' foods than in early childhood. Similarly, energy intake and consumption of several macronutrients increased over time in children of women with ED, compared to the unexposed group. It could be hypothesised that these findings reflect the influence of other societal effects on diet, such as school, or this might reflect the child taking more control over his/her own diet in late childhood. Alternatively, these findings may reflect ED-specific maternal feeding styles in early childhood. It has previously been reported that mothers with ED display more restrictive and controlling feeding styles (Park, et al., 2003; Patel, et al., 2002); increasing evidence suggests that parental restriction of their child's access to high fat and palatable foods may actually increase the desirability of such foods when they are available, leading to disinhibited eating

These findings of changes in dietary patterns and macronutrient consumption throughout childhood in children on women with ED are important, and require further investigation, since disinhibited eating styles in middle childhood may increase the risk of overeating and weight gain later in life (Clark, Goyder, Bissell, Blank, & Peters, 2007; Fisher & Birch, 1999; Johnson & Birch, 1994).

4.5.4 Gender differences

While some previous studies have indicated that maternal transmission of weight concerns and dieting behaviours may be stronger for girls than boys (Edmunds & Hill, 1999; Smolak, Levine, & Schermer, 1999), this finding has not always been supported. In the present investigation, female children of mothers with AN were more likely to adhere to the "health conscious" dietary pattern than males, suggesting a stronger maternal influence on this dietary pattern for female children of women with AN. It will be important to determine whether this translates into an increased risk for the development of disordered eating in girls of mothers with AN.

4.5.5 Strengths and limitations

This study is the first to systematically examine dietary patterns and nutrient intake across early and middle childhood in children of women with ED. The present study involved a substantially larger number of mothers and children, who were assessed at multiple time points in childhood, than previous investigations. Furthermore, due to the large sample size; it was possible to distinguish between different ED. Assessment of dietary patterns derived from PCA allowed a more interpretable investigation of the whole-diet of the children and to take into account the relationship between individual food items, as opposed to investigating individual food items.

However, there are some limitations to the study, which require consideration when interpreting the findings. This study is subject to the general limitation of outlined in the general ALSPAC general methodological considerations (section 2.4.5). In addition, maternal report was used to assess children's dietary intake. Women with ED often have difficulty evaluating their own dietary intake, and it is possible that women in these groups in particular were more likely to over or underestimate their child's consumption of certain foods. Another weakness of the present investigation was that standard portion sizes were used to assess nutrient intakes from the FFQ. Furthermore, although dietary patterns derived from the PCA were, in general, consistent across time points there was inevitably some variation. Therefore, changes in dietary pattern scores reflect both actual changes in children's diet and subtle variations within the dietary patterns over time (Northstone & Emmett, 2008).

4.5.6 Conclusions and clinical implications

The present investigation highlights several new findings regarding the diet of children of mothers with ED, which could have important implications for their eating habits, growth and development later in life. Further research is necessary to investigate the long-term outcomes of greater adherence to a 'health conscious' dietary pattern in children of women with ED, as well as the effects of this pattern on future risk for disordered eating or a rebound effect once children take more control over their diet. Furthermore, changes in adherence to dietary patterns and increasing macronutrient consumption over childhood may increase the risk of weight gain and disordered eating later in life.

Further research is needed prior to making specific clinical recommendations regarding dietary intake in children of women with ED. Nevertheless, clinicians' should be aware when working with mothers with ED that catering for their child's nutritional needs may be an area of difficulty, and additional support and guidance may be required and should be provided when necessary.

Chapter 5. Growth Trajectories in Children of Mothers with Eating Disorders: A Longitudinal Investigation

5.1 Introduction

As highlighted in the previous chapters, increasing research suggests that children of women with ED have an elevated risk of feeding and eating difficulties (Park, Senior, & Stein, 2003; Patel, et al., 2002). The findings from the previous chapter indicate that children of women with ED also have differential dietary patterns and macronutrient consumption during childhood, compared to children of women without an ED. Given these findings, it is important to consider the potential associations between maternal ED and growth in their children.

Findings from the literature review (Chapter 1, section 1.12) indicated that maternal ED, particularly AN, during pregnancy are associated with an increased risk of intrauterine growth restriction and small birth weight deliveries (Micali, Simonoff, et al., 2007a; Treasure & Russell, 1988). Conversely, it has recently been reported that women with BED during pregnancy are more likely to deliver babies that are large for gestational age (Siega-Riz, et al., 2010). Although preliminary studies have suggested adequate post-natal catch up growth in favourable environments (Stein & Woolley, 1996; Waugh & Bulik, 1999), others indicate that altered growth patterns may continue throughout infancy and childhood (Stein & Fairburn, 1989; van Wezel-Meijler & Wit, 1989; Timimi & Robinson, 1996).

While studies of children of women with AN have generally highlighted reduced growth in their children (Hodes, et al., 1997; Timimi & Robinson, 1996; van Wezel-Meijler & Wit, 1989), there is some evidence that maternal BN is associated with more rapid growth or obesity (Hodes, et al., 1997; Micali, et al., 2009; Stein & Fairburn, 1989), however few studies have investigated samples of women with both AN and BN. Furthermore, the majority of previous investigations have been limited by small sample size and include children at different ages, making the findings difficult to generalise.

Only one previous investigation has longitudinally investigated the growth of children of women with ED, which found children of women with ED had lower weight gain at one year compared to controls (Stein, et al., 1994); when the children

were followed up at ten years of age the BMI of the children born to mothers with ED were comparable to the control group (Stein, Woolley, Cooper, et al., 2006). Further longitudinal studies of growth in children of women with ED are necessary in order to investigate whether differences in growth of children whose mothers have ED are confined to infancy or are more persistent throughout childhood.

5.2 Aims and hypotheses

The aim of this study was to determine whether the growth trajectories: height, ponderal index (PI) and BMI from birth until ten years of age differ between children of women with and without ED in a prospective population-based cohort. Furthermore, this investigation aimed to explore whether any associations of maternal ED with growth in their children were specific to ED. In order to do this a further comparison group of women with other psychiatric disorders are included in the analyses. Specifically this study aimed to investigate:

1. growth trajectories: height, PI and BMI from birth until ten years of age, in children of women with ED, compared to children of women without a history of an ED;

2. whether any associations of maternal ED with growth in their children were specific to maternal ED, or comparable to growth trajectories in children of women with other psychiatric disorders;

3. the effect of ED sub-type and child gender on growth trajectories from birth until ten years of age, in children of women with ED, compared to children of women without a history of an ED, and children of women with other psychiatric disorders.

Hypothesis under investigation

1. Children of women with AN will be shorter and have lower PI and BMI, compared to children of women with other psychiatric disorders and women without a history of an ED.

2. Children of women with BN will have higher BMI throughout childhood, compared to children of women with other psychiatric disorders and women without a history of an ED.

3. Greater differences in growth trajectories will be apparent in female children of women with ED, compared to male children.

5.3 Methods

5.3.1 Design and participants

This study is based on data collected from ALSPAC (Golding, et al., 2001). Full details of the methodology are discussed in Chapter 2.

Women were grouped according to self-reported ED and other psychiatric diagnoses classification at 12 weeks gestation, as described in section 2.4.4 of Chapter 2 . Of the women reporting an ED, 171 (1.5%) women responded yes to the question 'have you ever had AN', 199 (1.8%) reported that they had suffered from lifetime BN and an additional 82 (0.7%) responded yes to both having ever had AN and BN (AN+BN). The questionnaire also enquired about a recent or past history of psychiatric problems including depression, schizophrenia, and alcoholism (n = 1,166, 9.5%). Women reporting a history of psychiatric problems other than an ED formed a comparison group. Of these women: 47 reported a history of drug addiction, 85 reported alcoholism, 4 women reported schizophrenia, 954 severe depression and 234 reported other psychiatric problems. The remaining women who did not report a history of ED or any other psychiatric diagnoses (n = 10,636; 86.8%) formed the unexposed comparison group.

Only singleton births were included in this investigation, and women were excluded from the present investigation if they did not respond to the questionnaire at 12 weeks gestation enquiring about their psychiatric history, or if insufficient data were available on their child's growth, see section 5.4.1 for full details on missing data.

5.3.2 Measures and Materials

The present investigation is based upon children's anthropometric data, collected from: self-report in questionnaires, direct measurements taken at children in focus and ALSPAC clinics and data extracted from health visitor records.

Anthropometric measures

Birth weight was extracted from the medical records, and birth length was measured by ALSPAC staff who visited newborns soon after birth (median 1 day, range 1-14 days), using a Harpenden Neonatometer.

Height and weight data were extracted from health visitor records, parental report from questionnaires, and measurements from clinic attendances. At the clinics between four months and five years, crown-heel length for children aged 4 to 25 months was measured using a Harpenden Neonatometer and from 25 months onwards standing height was measured using a Leicester Height Measure; weight was measured using Fereday 100kg combined scale (4 month clinic), Soenhle scale or Seca scale model 724 (8 month clinic), Seca 724 or Seca 835 (12 month clinic), Seca 835 (18 months onwards).

From age seven years upwards, all children were invited to annual clinics, at which standing height was measured to the last complete mm using the Harpenden Stadiometer and weight was measured to the nearest 0.1kg using the Tanita Body Fat Analyser (Model TBF 305).

PI was calculated as weight (kg) divided by height (m) cubed, and BMI was calculated as weight (kg) divided by height (m) squared.

5.3.3 Procedures

Socio-demographic data

Socio-demographic factors (gestational age, maternal age, maternal education, parity) previously associated with childhood growth and known to affect the outcome variables, were included in the models as confounding variables in the analyses. In order to investigate potential mediating factors pre-pregnancy, BMI and smoking during pregnancy were tested in all models in a second stage of analysis. These variables were obtained via maternal self-report during pregnancy, a full description of the socio-demographic factors included in this investigation and how the data were handled is outlined in Chapter 2.

Statistical analyses of growth trajectories [11]

The number of growth measurements and the child's age at which the measurements were taken was very variable between children. Therefore, a methodology was required to create comparable growth variables for each child, regardless of when and how often they were measured; multi-level modelling is one way to do this.

Individual growth trajectories were modelled using multi-level models with two levels: measurement occasion and individual, in the statistical package MLwiN (Rasbash, Charlton, Browne, Healy, & Cameron, 2005) using fractional polynomials to identify the best-fitting curves (Royston et al. 1999); the full methodology is presented in Appendix A. Such models allow for the change in scale and variance of height over time and use all available data from all eligible children under a missing at random assumption. They also allow for individual variation in growth trajectories, as random effects allow each individual to have different intercepts and slopes.

Differences in growth trajectories by maternal ED group were estimated by fitting interaction terms in the random effects models between maternal ED group and the constant term (representing birth length, PI at birth or BMI at age two) and each of the polynomial terms. This generates separate average growth trajectories for children whose mothers reported AN, BN, other psychiatric disorders, and the unexposed group. Growth trajectories are plotted to visually assess differences by ED group. Random effects models are used to predict the average height, PI, and BMI at different ages across childhood for children from each maternal ED group and for the children of women with other psychiatric disorders.

Childhood anthropometric values presented in the results were predicted from the multilevel models, and represent the predicted anthropometry for offspring of mean gestational age (39.4 weeks) and with a mother with the following characteristics: mean age (28.2 years), less than O-level education, parity of zero, mean pre-pregnancy BMI (22.94kg/m^2), non-smoker during pregnancy. Z-tests were then used

[11] The statistical procedures undertaken in this chapter were carried out in collaboration with Laura Howe, Research Associate Epidemiologist and Statistician at Bristol University.

to assess the statistical evidence for the differences comparing each group to children of women in the unexposed group.

Since growth trajectories during childhood vary according to child gender, and the effect of a maternal ED on growth may differ according to child gender, growth trajectories were modelled separately for boys and girls. Patterns of BMI change in early childhood are extremely complicated, given this PI (kg/m^3) was used as the measure of growth from birth to two years and BMI (kg/m^2) was modelled from two to ten years. Height was modelled from birth to ten years. Implausible height and weight measurements (>4 SD from the mean for gender and age specific category, approximately 0.1% of all measurements) were re-coded as missing.

It has been demonstrated in previous work that health visitor measurements of height and weight have good accuracy (Howe, Tilling, & Lawlor, 2009), but measurements recorded by the children's carers in questionnaires are likely to be less accurate (Dubois & Girad, 2007). Since measurements included in this investigation were drawn from a variety of sources, a binary indicator of measurement source (research clinic or health records versus questionnaire) was included in all models.

Associations between maternal ED and childhood growth trajectories were assessed in models adjusted for standard confounders (gestational age, maternal age, maternal education, and parity) previously found to affect childhood growth were included in the models. At a second stage, confounders and factors considered to be possible mediators (maternal pre-pregnancy BMI and smoking during pregnancy) were included in the model.

5.4 Results

Socio-demographic Data

Table 5.1 outlines the maternal characteristics of women with and without a history of ED. Child gender and maternal age were comparable across groups. The pre-pregnancy BMI of women with AN (21.3 kg/m^2) and AN+BN (21.5 kg/m^2) was lower than women in the unexposed group (22.9 kg/m^2) and women with BN (22.9 kg/m^2) and other psychiatric disorders (23.1 kg/m^2). Women reporting other psychiatric disorders were less likely to be educated to a degree level, whereas mothers with ED were likely to have spent more time in education.

Table 5.1: Socio-demographic of mothers and children included in the ponderal index model by maternal group

		Unexposed group	**AN**	**BN**	**AN+BN**	**other psychiatric disorders**	**p value**
N (%)		*8900 (87.3)*	*137 (1.3)*	*165 (1.6)*	*68 (0.7)*	*920 (9.0)*	
Male offspring, N(%)		4537 (51.0)	73 (53.3)	84 (50.9)	38 (55.9)	496 (53.9)	p=0.96
Maternal education, N(%)	< O-Level	2397 (26.9)	33 (24.1)	35 (21.2)	11 (16.2)	341 (37.1)	
	O-Level	3169 (35.6)	35 (25.6)	58 (35.2)	16 (23.5)	330 (35.9)	
	A-Level	2114 (23.8)	38 (27.7)	46 (27.9)	24 (35.3)	164 (17.8)	
	Degree	1220 (13.7)	31 (22.6)	26 (15.8)	17 (25.0)	85 (9.2)	p=0.13
Maternal parity, mean (SD)		0.81 (0.97)	0.89 (1.10)	0.78 (1.00)	0.87 (1.02)	0.98 (1.11)	p=0.93
Maternal pre-pregnancy BMI (kg/m^2), mean (SD)		22.96 (3.81)	21.36 (2.91)	22.93 (3.93)	21.53 (3.10)	23.11 (4.05)	p<0.001
Maternal age (years)		28.44 (5.40)	29.13 (4.77)	28.32 (4.77)	29.31 (4.64)	28.46 (5.40)	p=0.35

** p<0.001; * p<0.05

N.B. shown for the 10,190 children included in ponderal index models

5.4.1 Missing data

Table 5.2 provides a summary of the number of children with growth data available, the total number of measurements available and the mean number of measurements per child included in the growth models.

Data included in the height models were 10,315, 73.6% of the full ALSPAC cohort alive at 1 year. Data included in the PI model were available on 10,190 and BMI was available on 9,591 children, 72.7% and 68.5%, respectively, of the full ALSPAC cohort alive at 1 year. There was a median of seven growth measurements per child, with most children having at least one measurement in each growth period.

Table 5.2: Summary of measurements included in the growth model for 12,366 participants included in models

	Number of children with anthropometry data	Total number of measurements	Median (IQR) number of measurements per child
Height			
Overall	10,315	86,368	7 (5,10)
Birth	7,972	7,972	N/A
Birth to two years	10,042	36.281	3 (2 4)
Two to five years	8,487	16,341	1 (1,2)
Five to ten years	8,008	25,774	3 (2,4)
Ponderal Index			
Overall	10,190	42,665	4 (3,5)
Birth	7,837	7,837	N/A
Birth to two years	10,028	34,562	3 (2,4)
Body Mass Index			
Overall	9,591	37.885	4 (2,5)
Two to five years	8,266	14.047	1 (1,2)
Five to ten years	8,008	25,774	3 (2,4)

In order to investigate the representativeness of the participants included in the growth models, socio-demographic characteristics of the children included in the PI models were compared to the full ALSPAC cohort. The results of this investigation are shown in Table 5.3. Children included in the PI models investigated in this chapter had mothers who had spent slightly more time in education, had a slightly longer birth

length and higher birth weight. No differences in child gender or maternal BMI were apparent between the children included in the PI model and the full ALSPAC sample.

Table 5.3: Characteristics of participants included in this study and the full ALSPAC cohort

	Participants included in PI models (N=10,190)	Full ALSPAC cohort (children alive at 1 year, N=13,998)	*p* value
Female	4 962 (48.7%)	6 774 (48.4%)	0.65
Maternal education			
Less than O-Level	2 817 (26.7%)	3 731 (30.0%)	
O-Level	3 608 (35.4%)	4 303 (34.6%)	
A-Level	2 386 (23.4%)	2 794 (22.5%)	
Degree or above	1 379 (13.5%)	1 600 (12.9%)	0.001
Birth length (cm), mean (SD)	50.75 (2.39)	50.59 (2.48)	<0.001
Birth weight (kg) , mean (SD)	3.44 (0.52)	3.39 (0.56)	<0.001
Maternal pre-pregnancy BMI (kg/m^2), mean (SD)	22.94 (3.83)	22.94 (3.85)	0.99

5.4.2 Birth length and height differences across eating disorder group

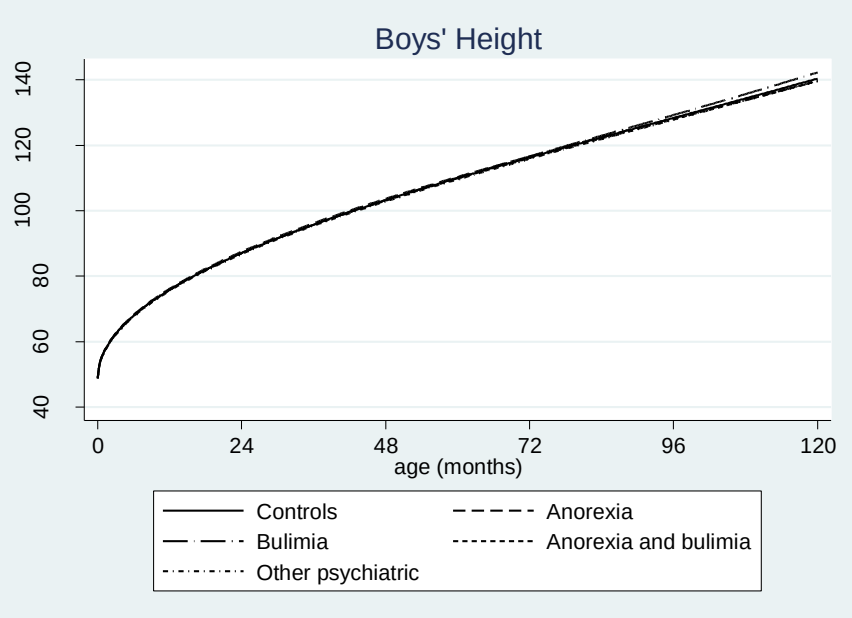
Some gender specific differences in growth were found in children of women with ED, statistical evidence of growth differences existed for some but not all of the growth periods studied; in many cases the coefficients had large standard errors, which is unsurprising given the small number of children in each maternal ED group. Therefore, patterns of growth and differences in predicted values are discussed in addition to statistical significance throughout this results section.

Male children

Figure 5.1 displays the average height trajectories for boys by maternal ED, after adjustment for confounders. Predicted heights (Table 5.4) calculated from multi-level models indicated that male children of women in the AN group and the BN group tended to be slightly taller than children in the unexposed group throughout

childhood. Only small differences were observed in early childhood, the difference widened with age and by 10 years children of women with BN were on average 1.8 cm (p=0.01) taller than children in the unexposed group. No substantial change to the association was observed when potential mediators were included in the model, Table 5.4.

Figure 5.1: Average fractional polynomial curve of height trajectories for boys by maternal eating disorder, birth to ten years, adjusted for confounders



In contrast, children of women reporting other psychiatric disorders were found to be shorter throughout childhood, Table 5.4. At 5 years of age the predicted height of children of women with other psychiatric disorders was on average 0.41 cm shorter (p=0.04) and 0.64 cm shorter (p=0.06) at 10 years of age than the children in the unexposed group. Entering potential mediating factors into the final model made only a fairly small difference to the association, see Table 5.4.

Male children of women with AN+BN were also shorter than children in the unexposed group, although differences were small. When potential mediators were entered into the model the pattern of height differentials changed for children of women with AN+BN, who were taller than the unexposed group in early childhood, but remained shorter after 5 years of age, Table 5.4.

Table 5.4: Predicted height of male children by categories of maternal eating disorder

	Unexposed group	**AN**	**BN**	**AN+BN**	**other psychiatric disorders**
Height (cm)	***N=4588***	***N=74***	***N=85***	***N=38***	***N=501***
Model 1.		**Mean difference (SE) from controls**			
Birth	50.26 (0.08)	+0.137 (0.236) p=0.55	+0.174 (0.226) p=0.43	-0.102 (0.322) p=0.73	-0.198 (0.097) p=0.04
1 year	76.10 (0.08)	+0.327 (0.280) p=0.24	+0.051 (0.264) p=0.26	-0.094 (0.384) p=0.79	-0.284 (0.113) p=0.01
2 years	87.32 (0.08)	+0.400 (0.354) p=0.25	+0.011 (0.333) p=0.95	-0.095 (0.485) P=0.82	-0.323 (0.143) p=0.02
5 years	110.22 (0.10)	+0.391 (0.518) p=0.44	+0.151 (0.488) p=0.74	-0.173 (0.710) p=0.79	-0.416 (0.210) p=0.04
10 years	140.68 (0.13)	-0.716 (0.845) p=0.38	+1.883 (0.812) p=0.01	-0.814 (1.149) p=0.46	-0.643 (0.352) p=0.06
Model 2.					
Birth	50.33 (0.08)	+0.210 (0.234) p=0.29	+0.165 (0.224) p=0.45	+0.042 (0.320) p=0.87	-0.125 (0.097) p=0.19
1 year	76.18 (0.08)	+0.400 (0.279) p=0.14	+0.050 (0.263) p=0.83	+0.047 (0.383) p=0.88	-0.209 (0.114) p=0.06
2 years	87.39 (0.08)	+0.473 (0.354) p=0.17	+0.013 (0.333) p=0.94	+0.044 (0.485) p=0.90	-0.247 (0.144) p=0.08
5 years	110.30 (0.10)	+0.465 (0.518) P=0.36	+0.159 (0.488) p=0.72	-0.036 (0.710) p=0.94	-0.337 (0.211) p=0.10
10 years	140.76 (0.13)	-0.641 (0.844) P=0.43	+1.892 (0.812) p=0.01	-0.665 (1.149) p=0.55	-0.555 (0.352) p=0.11

Model 1: Adjusted for confounders: gestational age, maternal age, maternal education, parity;

Model 2: Adjusted for confounders and potential mediators: maternal pre-pregnancy BMI and smoking during pregnancy.

Female children

Predicted height values at all ages for female children of women with AN and AN+BN were smaller compared to children in the unexposed group, Table 5.5. As shown in Figure 5.2, height differences during childhood were small between the maternal groups.

On average, female children of women with AN had a predicted birth length of 0.47 cm (p=0.07) shorter and at 10 years the predicted height of children in this group was 0.57 cm (p=0.55) shorter than children in the unexposed group. See Table 5.5. By comparison, female offspring of women reporting AN+BN were slightly longer at birth than the unexposed group (difference 0.23 cm, p=0.52), but by 2 years they were on average 0.93 cm (p=0.08) shorter than the unexposed group, and by 10 years they were 0.94 cm shorter (p=0.22). When pre-pregnancy BMI and smoking in pregnancy were entered into the model these patterns remained, see model 2 in Table 5.5.

Figure 5.2: Average fractional polynomial curve of height trajectories for boys by maternal eating disorder, birth to ten years, adjusted for confounders

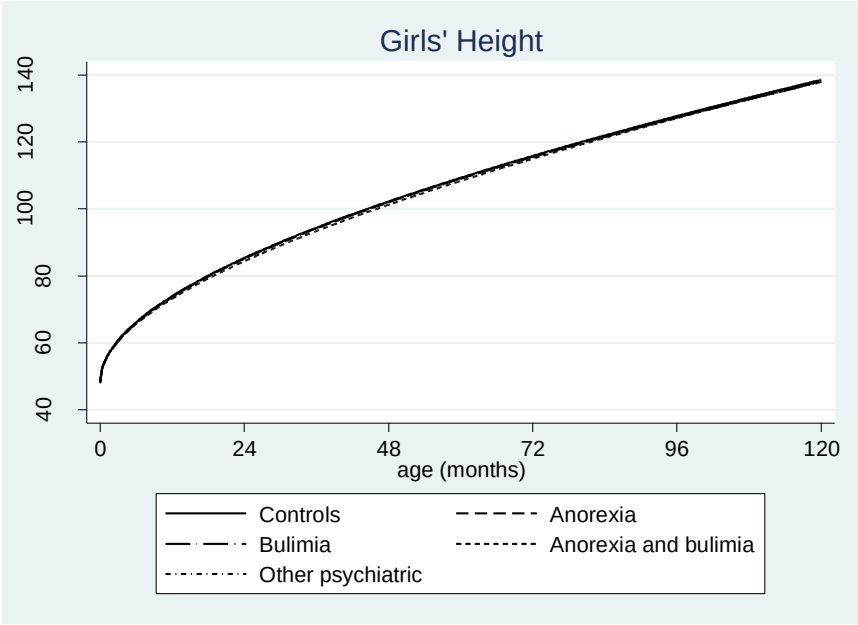


Table 5.5: Predicted height of female children across categories of maternal eating disorder

	Unexposed group	**AN**	**BN**	**AN+BN**	**other psychiatric disorders**
Height (cm)	***N=4416***	***N=65***	***N=82***	***N=30***	***N=432***
Model 1.			**Mean difference (SE) from controls**		
Birth	***N=4416***	***N=65***	***N=82***	***N=30***	***N=432***
1 year	49.73 (0.08)	-0.471 (0.265) p=0.07	-0.078 (0.235) p=0.72	+0.231 (0.371) p=0.52	-0.161 (0.107) p=0.12
2 years	74.25 (0.08)	-0.265 (0.300) p=0.36	+0.048 (0.269) p=0.84	-0.732 (0.437) p=0.13	-0.184 (0.124) p=0.13
5 years	85.63 (0.08)	-0.240 (0.372) P=0.50	+0.020 (0.334) p=0.93	-0.931 (0.540) p=0.08	-0.184 (0.153) p=0.22
10 years	109.61 (0.09)	-0.309 (0.536) p=0.55	-0.184 (0.478) p=0.68	-0.937 (0.773) p=0.22	-0.168 (0.220) p=0.43
Model 2.					
Birth	49.79 (0.08)	-0.412 (0.263) P=0.11	-0.037 (0.233) p=0.85	+0.295 (0.368) p=0.41	-0.088 (0.107) p=0.40
1 year	74.31 (0.08)	-0.203 (0.301) p=0.49	+0.091 (0.269) p=0.72	-0.676 (0.437) p=0.11	-0.112 (0.124) p=0.35
2 years	85.69 (0.08)	-0.179 (0.373) p=0.61	+0.062 (0.334) p=0.83	-0.876 (0.541) p=0.10	-0.112 (0.154) p=0.45
5 years	109.67 (0.09)	-0.250 (0.536) p=0.62	-0.142 (0.478) p=0.75	-0.879 (0.773) p=0.25	-0.097 (0.221) p=0.64
10 years	138.92 (0.13)	-0.519 (0.865) p=0.53	-0.611 (0.762) p=0.41	-0.256 (1.229) p=0.81	-0.052 (0.359) p=0.86

Model 1: Adjusted for confounders: gestational age, maternal age, maternal education, parity;

Model 2: Adjustment for confounders and and potential mediators: maternal pre-pregnancy BMI and smoking during pregnancy

Female children in the other psychiatric disorder group also tended to be shorter throughout childhood; however these differences were of a lower magnitude than the differences observed for the AN and AN+BN groups, see Table 5.5. By comparison, female children of women with BN tended to be slightly taller throughout childhood compared to children in the unexposed group in models including both confounding and mediating variables, See Table 5.5.

5.4.3 PI and BMI differences across maternal eating disorder groups

Figure 5.3 illustrates the PI and BMI trajectories of male children of women with ED, compared to both the unexposed group and children of women with other psychiatric disorders.

Male children

Ponderal Index

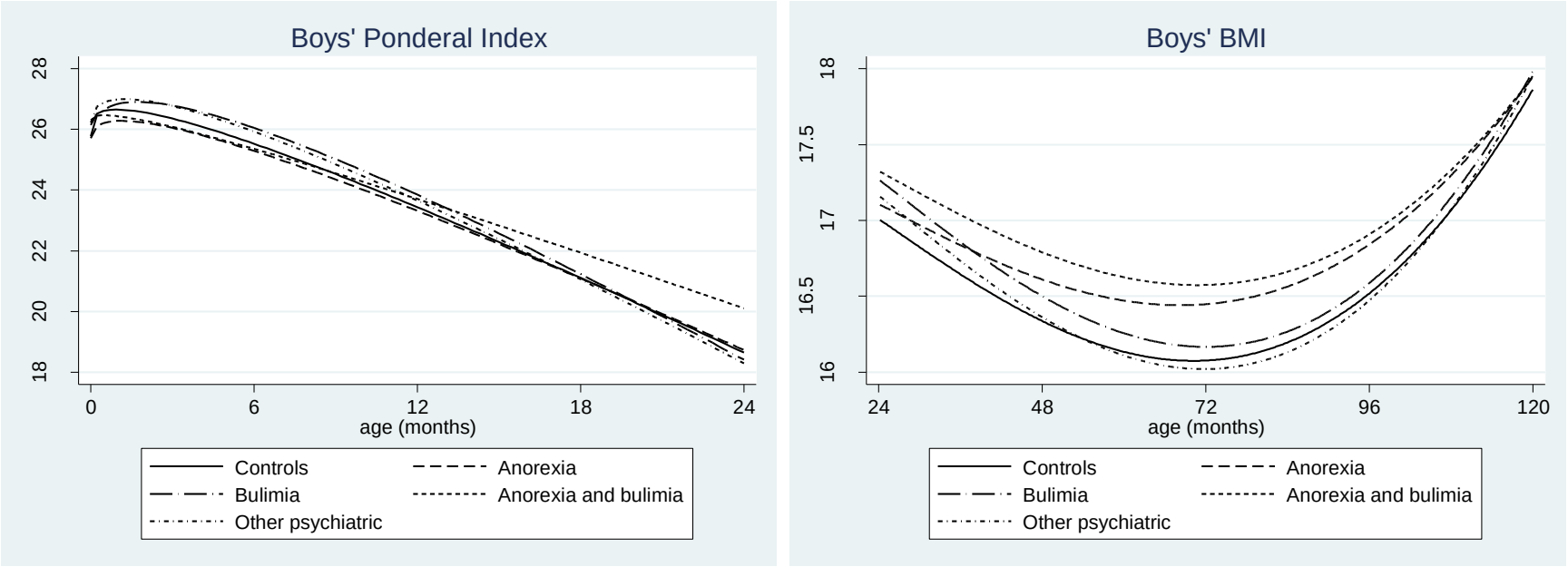
PI, from birth to one year, were slightly lower in male children of women with AN (-0.43, p=0.13) and BN (-0.28, p=0.32), but comparable in children of women with AN+BN (+0.069, p=0.84). See Figure 5.3. and Table 5.6. By one year the PI of children of women with AN and AN+BN remained comparable to children in the unexposed group. As shown in Table 5.6 and Figure 5.3, the largest difference in PI was observed in male children of women with BN, who had a predicted PI of 0.41 kg/m^3 (p=0.09) larger than children in the unexposed group at one year. This pattern persisted when controlling for maternal BMI and smoking, Table 5.6. Male children of mothers with other psychiatric disorders also tended to have higher PI between birth and two years, although the increase in PI was less than for the male children of women with BN. At birth the predicted PI of children in the other psychiatric disorder group was 0.12 kg/m^3 (p=0.29) higher than males in the unexposed group, and 0.22 kg/m^3 (p=0.03) higher at one year. After entering potential mediators into the model, these difference remained.

Body Mass Index

As shown in Figure 5.3, between the ages of 2 and 10 years, male children of women in all ED groups had higher BMI than children in the unexposed group. The largest differences were observed at 5 years of age in children of women with AN, whose predicted BMI was 0.33 kg/m^2 (p=0.04) higher, than children in the unexposed group.

At 10 years the BMI of male children of women with AN and AN+BN were more comparable to children in the unexposed group, see Table 5.6. These differences persisted after pre-pregnancy BMI and smoking were included in the model. BMI trajectories of male children of women with other psychiatric disorders was higher at 2 years post-natal (+0.16 kg/m², p=0.09), but few differences were observed later in childhood when the children were 5 and 10 years. After entering potential mediators into the model this pattern remained similar, see model 2 in Table 5.6.

Figure 5.3: Average fractional polynomial curve of ponderal index (birth to two years) and body mass index trajectories (two to ten years) for boys by maternal eating disorder adjusted for confounders



Values are predicted from the multilevel models, and represent the predicted anthropometry for offspring of mean gestational age (39.4 weeks) and with a mother with the following characteristics: mean age (28.2 years), less than O-level education, parity of zero

Table 5.6: Predicted PI and BMI of male children by categories of maternal eating disorder

	Unexposed group	**AN**	**BN**	**AN+BN**	**other psychiatric disorders**
Model 1.		**Mean difference (SE) from unexposed group**			
PI (kg/m3)	***N=4537***	***N=73***	***N=84***	***N=38***	***N=496***
Birth	26.19 (0.08)	-0.428 (0.292) p=0.13	-0.277 (0.287) p=0.32	+0.069 (0.404) p=0.84	+0.127 (0.123) P=0.29
1 year	23.33 (0.07)	-0.119 (0.250) p=0.62	+0.406 (0.243) p=0.09	+0.270 (0.343) p=0.42	+0.216 (0.101) P=0.03
BMI (kg/m2)	***N=4271***	***N=68***	***N=78***	***N=35***	***N=452***
2 years	16.80 (0.06)	+0.099 (0.2410 p=0.66	+0.260 (0.226) p=0.24	+0.316 (0.295) p=0.27	+0.155 (0.093) p=0.09
5 years	15.93 (0.06)	+0.339 (0.169) P=0.04	+0.122 (0.159) p=0.43	+0.491 (0.233) p=0.03	-0.024 (0.069) p=0.71
10 years	17.65 (0.07)	+0.090 (0.394) p=0.80	+0.119 (0.388) p=0.82	+0.084 (0.543) p=0.85	+0.093 (0.169) p=0.57
Model 2.					
PI (kg/m3)	***N=4537***	***N=73***	***N=84***	***N=38***	***N=496***
Birth	26.22 (0.08)	-0.369 (0.292) p=0.20	-0.295 (0.286) p=0.29	+0.083 (0.403) p=0.82	+0.108 (0.122) p=0.36
1 year	23.35 (0.07)	-0.071 (0.250) p=0.76	+0.393 (0.243) p=0.10	+0.281 (0.343) p=0.40	+0.197 (0.102) p=0.05
BMI (kg/m2)	***N=4271***	***N=68***	***N=78***	***N=35***	***N=452***
2 years	16.84 (0.06)	+0.195 (0.241) p=0.41	+0.268 (0.225) p=0.22	+0.327 (0.294) p=0.26	+0.128 (0.093) p=0.16
5 years	15.96 (0.06)	+0.426 (0.166) p=0.01	+0.114 (0.156) p=0.45	+0.505 (0.228) p=0.02	-0.051 (0.068) p=0.44
10 years	17.69 (0.07)	+0.167 (0.387) p=0.65	+0.112 (0.381) p=0.75	+0.077 (0.532) p=0.86	+0.056 (0.166) p=0.72

Model 1: Adjusted for confounders: gestational age, maternal age, maternal education, parity;

Model 2: Adjustment for confounders and potential mediators: maternal pre-pregnancy BMI and smoking during pregnancy

Female children

Ponderal Index

As shown in Figure 5.4, the PI of female children of women with BN was higher than the unexposed group at birth (+0.48 kg/m^3, p=0.04). By 24 months this difference had

reduced and was no longer statistically significant (+0.06 kg/m^3, p=0.81), see Table 5.7. In comparison, the PI at birth in female children of women with AN (-0.07 kg/m^3, p=0.78) and AN+BN (-0.16 kg/m^3, p=0.66) was more comparable to children in the unexposed group, Table 5.7.

The PI of female children of women with other psychiatric disorders at birth was also comparable to children in the unexposed group (-0.09, p=0.40), and by 2 years was 0.22 kg/m^3 (p-0.09) lower compared to children in the unexposed group.

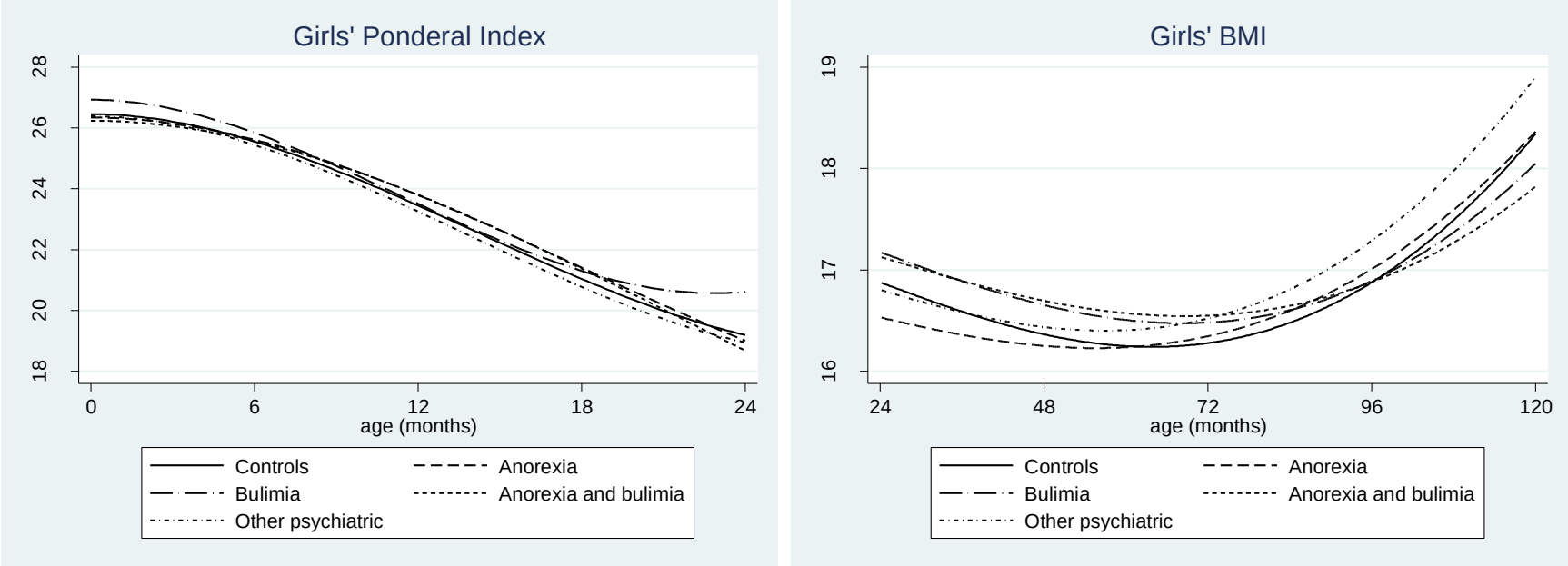
Body Mass Index

Female children of women with BN continued to have a higher BMI until 5 years, see Figure 5.4, but by 10 years their predicted BMI was 0.28 kg/m^2 lower than children in the unexposed group (p=0.45), Table 5.7.

Compared to female children in the unexposed group, female children of women with AN had a lower BMI in early childhood (24 to 48 months), but similar later in childhood (72 to120 months), see Figure 5.4. There was a trend for female children of women with AN to have a lower BMI (-0.34 kg/m^2, p=0.1) than the unexposed group at 2 years of age, which was weakened when potential mediators were included in the model (see model 2, Table 5.7). Female children of women with AN+BN also tended to have higher BMI in early childhood compared to children in the unexposed group (0.32 kg/m^2 higher at 5 years), but lower in later childhood. At 10 years of age children of women with AN+BN had a predicted BMI of 0.52 kg/m^2 (p=0.38) lower than children in the unexposed group.

The BMI trajectory of female children of women reporting other psychiatric disorders followed a slightly different pattern compared to children of women with ED, see Figure 5.4 and Table 5.7. In early childhood their BMI tended to be lower than children in the unexposed group, but higher in later childhood. At 10 years of age predicted BMI was on average 0.56 kg/m^2 (p=0.002) higher than the unexposed group

Figure 5.4: Average fractional polynomial curve of ponderal index (birth to two years) and body mass index (two to ten years) trajectories for girls by maternal eating disorder, adjusted for confounders



Values are predicted from the multilevel models, and represent the predicted anthropometry for offspring of mean gestational age (39.4 weeks) and with a mother with the following characteristics: mean age (28.2 years), less than O-level education, parity of zero

Table 5.7: Predicted PI and BMI of female children by categories of maternal eating disorder

	Unexposed group	**AN**	**BN**	**AN+BN**	**other psychiatric disorders**
Model 1.			**Mean difference (SE) from unexposed group**		
PI (kg/m^3)	***N=4363***	***N=64***	***N=81***	***N=30***	***N=424***
Birth	26.24 (0.08)	-0.070 (0.275) p=0.78	+0.480 (0.243) p=0.04	-0.162 (0.397) p=0.66	-0.090 (0.111) p=0.40
1 year	23.24 (0.08)	+0.397 (0.304) p=0.18	+0.061 (0.282) p=0.81	+0.386 (0.488) p=0.42	-0.220 (0.133) p=0.09
BMI (kg/m^2)	***N=4117***	***N=61***	***N=78***	***N=29***	***N=398***
2 years	16.61 (0.06)	-0.346 (0.245) p=0.15	+0.297 (0.217) p=0.22	+0.249 (0.334) p=0.43	-0.075 (0.104) p=0.46
5 years	15.98 (0.06)	-0.011 (0.195) p=0.93	+0.258 (0.172) p=0.13	+0.324 (0.277) p=0.23	+0.157 (0.082) p=0.05
10 years	18.07 (0.08)	+0.025 (0.445) p=0.93	-0.285 (0.386) p=0.45	-0.516 (0.606) p=0.38	+0.561 (0.187) p=0.002
Model 2.					
PI (kg/m^3)	***N=4363***	***N=64***	***N=81***	***N=30***	***N=424***
Birth	26.27 (0.08)	-0.115 (0.277) p=0.66	+0.473 (0.244) p=0.05	-0.215 (0.399) p=0.57	-0.070 (0.112) p=0.52
1 year	23.26 (0.08)	+0.338 (0.304) p=0.26	+0.052 (0.282) p=0.83	+0.349 (0.489) p=0.46	-0.201 (0.133) p=0.12
BMI (kg/m^2)	***N=4117***	***N=61***	***N=78***	***N=29***	***N=398***
2 years	16.66 (0.06)	-0.259 (0.244) p=0.28	+0.320 (0.217) p=0.25	+0.366 (0.333) p=0.26	-0.081 (0.104) p=0.42
5 years	16.04 (0.06)	+0.077 (0.191) p=0.87	+0.286 (0.168) p=0.08	+0.452 (0.270) p=0.09	+0.154 (0.080) p=0.05
10 years	18.13 (0.08)	-0.091 (0.437) p=0.81	-0.260 (0.379) p=0.48	-0.393 (0.594) p=0.49	+0.560 (0.184) p=0.002

Model 1: Adjusted for confounders: gestational age, maternal age, maternal education, parity;

Model 2: Adjustment for confounders and potential mediators: maternal pre-pregnancy BMI and smoking during pregnancy

5.5 Discussion

This study highlights differential patterns of growth in children of women with ED, compared to both children of women with no ED history and those with other psychiatric disorders. In general, differences in growth trajectories were small in this general population cohort, and suggest that previous case reports of 'wasting' (Hodes, et al., 1997) or 'failure to thrive'(Brinch, et al., 1988) in children of women with ED, may only apply to more severe cases of ED. However, there were some noteworthy differences in growth trajectories in children of women with ED, which require consideration.

5.5.1 Male children

In this study, increased growth was observed in male children of mothers in the BN group, who were taller throughout childhood compared to children of women with no ED. Similarly, male children of women with AN were taller between birth and ten years. In contrast, male children of women with other psychiatric disorders tended to be shorter throughout childhood, compared to children in the unexposed group.

Male children of women in all ED groups also had higher BMI in middle childhood, with the largest difference observed in children of women with lifetime AN at 5 years of age. In comparison, the BMI trajectory of male children of women with other psychiatric disorders was more comparable to children of women in the unexposed group. These findings suggests that the growth trajectories observed in male children during childhood, may be more specific to maternal eating pathology, rather than more general psychopathology.

Preliminary research has suggested that children of women with BN may have an increased risk of being overweight (Micali, et al., 2009) or obese (Hodes, et al., 1997) during childhood. For example, a previous investigation in this sample indicated that children of women with BN had a 1.8 increased risk of being overweight at nine months post-partum, compared to children of women without ED. Therefore, in line with the hypothesis, the present investigation suggests that accelerated growth persists into middle childhood in male children of women with ED, but did not appear to be specific to children of women with BN. Rapid growth in childhood may increase the risk of obesity and health problems later in life, it will therefore be important to follow up the health and development of these children during adolescence.

5.5.2 Female children

Female children of women with ED, particularly the children of women with lifetime AN (AN and AN+BN), tended to be shorter throughout childhood than children in the unexposed group. This finding is in line with previous research, which suggests children of women with AN may be at risk of experiencing reduced growth during childhood (Hodes, et al., 1997; Timimi & Robinson, 1996; van Wezel-Meijler & Wit, 1989), and highlights a potential increased risk of stunting in female children of women with AN (van Wezel-Meijler & Wit, 1989).

Despite evidence of reduced height in female children in all ED groups, compared to children in the unexposed group, BMI trajectories fluctuated throughout childhood and female children of women with BN and AN+BN tended to have higher BMI in early childhood but lower at 10 years of age. Conversely, children of women with AN tended to have lower BMI in early childhood but higher by the age of 10 years, although these differences were in general small.

5.5.3 Gender differences

The above findings highlight that the relationship between maternal ED and child growth is different for male and female children. Previous investigations have indicated that mothers with ED show greater concern for their daughter's weight and shape than sons (Agras, et al., 1999), furthermore female offspring have been found to have a higher risk of being underweight than male (Hodes, et al., 1997). These findings support the idea that growth trajectories of children of women with ED may be gender specific, however, since the growth models in the present investigation were constructed separately for males and females, it was not possible to formally test for gender interactions. Gender differences highlighted in this investigation should therefore be treated with caution, and require replication in other studies.

The BMI trajectory of female children of women with ED appeared to follow a slower developmental path with an earlier adipose rebound. This was particularly the case for female children of women with BN and AN+BN and resulted in higher BMI in early childhood, which was lower in later life. The long-term implications of this type of growth trajectory presently remains unclear, however a recent study of adult women with AN found that a larger BMI at two years and poor BMI acceleration after the adipose rebound were associated with an increased risk of AN later in life (Neveu, Neveu, Edouard, Nicolas, & Perroud, Submitted). Further research is necessary to

follow up the growth of these groups of children in order to investigate the long-term effects of this type of growth trajectory.

Alternatively, differences in growth observed in this study may be related to previously observed feeding difficulties or differential childhood dietary patterns reported in the previous chapter (Dietary Patterns and Macronutrient Intake in Children of Mothers with Eating Disorders). In the present investigation female children of women with AN were found to have a lower BMI between two and five years, which was higher at ten years. Findings from the previous investigation (Chapter 4) indicated that female children of women with AN in this sample showed greater adherence to a health conscious dietary pattern in early childhood, which had decreased by nine years of age. Therefore, patterns of growth in this group could reflect changes in dietary patterns across childhood. However, the relationship between dietary intake and childhood growth were not investigated in this thesis and therefore the relationship between the two remains unclear and requires further investigation.

Different growth trajectories were also apparent in children of women with ED compared to those whose mothers had another psychiatric disorder. Both male and female children of women reporting other psychiatric disorders were shorter. The BMI trajectory of male children of women with other psychiatric disorders was more comparable to the control group, whilst female children had higher BMI at five and ten years. Furthermore, the height differentials observed in children of women with ED tended to widen over childhood; in contrast, they were relatively consistent across time in children of women with other psychiatric disorders.

It has previously been reported that socioeconomic differences in childhood growth were relatively stable across childhood, suggesting that pre-natal, genetic and epigenetic effects on growth maybe important (Howe, et al., 2010). On the basis of these findings, it could be postulated that height differences in children of women with other psychiatric disorders are possibly driven by intra-uterine processes, whereas for the ED group differences are more likely to be both due to both intra-uterine processes and post-natal factors, such as feeding and diet. Factors contributing to childhood growth are likely to involve a combination of genetic and environmental factor, and further research examining the potential mechanisms of the growth differentials observed in this study will be important.

5.5.4 Strengths and limitations

This study is the first study to longitudinally investigate growth in children of women with ED in a general population cohort, and additionally to distinguish between different ED classifications. Furthermore, the availability of data on important confounding and mediating factors allowed a less biased investigation of relevant outcomes across ED, and the ability to compare growth in children of women with ED to children of women with other psychiatric disorders and a group of unexposed children.

Previous studies in children of women with ED have often only investigated growth in early childhood in clinical samples, or reported on measurements taken at a single time-point. The main strengths of this study are its uniqueness in examining growth trajectories from birth to ten years of age, in a large sample size with a large number of repeated measurements. The modelling approach used in this investigation has allowed for the examination of growth trajectories across childhood, taking account of the different timings and numbers of measurements between children.

However, there are some limitations to this study, which require consideration when interpreting the results. The factors affecting childhood growth are complex and multifaceted, including several environmental and genetic factors that were beyond the scope of the investigation presented in this chapter. Therefore, it is possible that the findings of this study could be due to other factors that were not investigated. Most notably, since the focus of this chapter was to investigate the role of maternal ED on childhood growth, paternal factors, which are likely to influence childhood growth, were not studied.

As highlighted in the ALSPAC general methodological considerations of Chapter 2 (section 2.4.5.) The classification of ED was made on the basis of maternal self-report, which may be subject to bias or inaccurately estimate the prevalence of ED. A second limitation is that maternal ED classification was made on the basis of lifetime history and it is not possible investigate the associations of current ED symptoms and childhood growth. Furthermore, the number of women within each of the ED groups was relatively small, and it is therefore possible that negative findings are a result of small sample size, particularly for the smallest (AN + BN) group.

5.5.5 Conclusions and clinical implications

In conclusion, the present investigation highlights several new findings regarding the growth of children of mothers with ED. Reassuringly, differences in growth trajectories were, in general, small in this general population cohort compared to some previous investigations of children of mothers with ED in clinical samples (e.g. Brinch, et al., 1988; Hodes, et al., 1997; van Wezel-Meijler & Wit, 1989). Nevertheless, the findings from the present investigation indicate some gender specific alterations to growth trajectories in children of women with ED.

These findings, in combination with previous reports in clinical samples, indicates that paediatricians and clinicians' working with mothers who have a history of ED should be aware of the potential for differential patterns of growth in their children, in order to monitor their health and development. Early childhood growth has been found to predict growth and weight gain later in adolescence and adulthood, and may be linked to later development of ED; therefore further investigation of their growth and development during adolescence will be important.

Chapter 6. Maternal Psychopathology and Stress in Pregnancy in Women with Eating Disorders

6.1 Introduction

6.1.1 Eating disorders and pregnancy

As highlighted in the main literature review of this thesis (Chapter 1), research suggests that women with ED tend to experience an improvement of symptoms during pregnancy (Micali, Treasure, et al., 2007b; Morgan, et al., 1999c). Nevertheless, there is increasing evidence that the risk for obstetric complications, such as small birth weight and prematurity, is elevated in women with ED (Abraham, 1998; Brinch, et al., 1988; Bulik, et al., 1999; Ekeus, et al., 2006; Koubaa, et al., 2005; Mazzeo, et al., 2006; Micali, Simonoff, et al., 2007a; Morgan, et al., 2006; Sollid, et al., 2004). However, few studies have investigated the potential underlying mechanisms for obstetric complications in women with ED.

6.1.2 Stress physiology

One proposed mechanism for the elevated risk of obstetric complications in women with ED is via foetal overexposure to stress hormones, such as cortisol (Micali & Treasure, 2009). Co-morbid psychiatric illnesses, such as anxiety and depression, are common in women experiencing an ED (Hudson, et al., 2007), despite this, few studies have investigated levels of co-morbid psychopathology, particularly anxiety, during pregnancy in women with ED. Furthermore, no studies to date have investigated psychobiological measures of stress during pregnancy in women with ED.

6.2 Aims and hypotheses

The overall aim of this study was to investigate maternal psychopathology (ED symptoms and behaviours, depression and anxiety) and stress (perceived stress and diurnal cortisol rhythms) during pregnancy in women with active and remitted ED, compared to a healthy control group. Furthermore, this study aimed to explore the relationship between maternal psychopathology and cortisol levels during pregnancy in these three groups of women. Specifically this study aimed to investigate:

1. changes in ED psychopathology, stress anxiety in depression in early and late pregnancy, in women with active and remitted ED, compared to a healthy control group;

2. diurnal cortisol levels in mid and late pregnancy, in women with active and remitted ED, compared to a healthy control group;

3. the relationship between cortisol and maternal psychopathology during pregnancy in women with active and remitted ED, compared to a healthy control group.

Hypothesis under investigation

1. Women with active and remitted ED will have a reduction ED symptoms and an increase in anxiety, depression, and stress during pregnancy.

2. Women with active ED will have high levels of salivary cortisol and abnormal circadian cortisol profiles during pregnancy, compared to women with past ED and healthy controls.

3. High levels of psychopathology during pregnancy will predict elevated cortisol levels in women with ED.

6.3 Methods

6.3.1 Design and participants

This study is based on data collected as part of the NEST-p study, see NEST-p methodology chapter (Chapter 2, section 2.5) for full details of the methods, and consists of a core sample 88 participants who provided data during pregnancy.

Between April 2009 and September 2011, participants were recruited from three main sources: Women's Services at KCH in South London, Perinatal Psychiatry services and specialist ED services within SLaM. Eligible participants were classified according to ED diagnosis; full details of group classification of the participants in this chapter see Chapter 2, section 2.5.4 . Twenty-seven women met criteria for an active ED (current ED group), 26 women met criteria for a past ED (recovered ED group) and 35 women had never met criteria for a psychiatric disorder (healthy control group).

6.3.2 Outcomes and measures

Full details of the measures used within this investigation, including validity and reliability, are described in the general methodology of Chapter 2.

Psychiatric diagnoses

Maternal ED and co-morbid diagnoses was ascertained using the SCID-I for DSM-IV-TR disorders (First, et al., 2002).

Maternal psychopathology

Self-reported ED symptoms during pregnancy were assessed using the EDE-Q (Fairburn & Bèglin, 1994). Self-reported depression, perceived stress, state, trait and pregnancy related anxiety, were assessed using: BDI (Beck, et al., 1961) PSS (Cohen, et al., 1983), STAI (Spielberger, et al., 1983) and PRAQ-R (Huizink, Mulder, Robles de Medina, et al., 2004), respectively.

Maternal Cortisol

In order to investigate physiological levels of stress during pregnancy, women were asked to provide saliva samples during pregnancy, from which concentrations of salivary cortisol were measured. Maternal cortisol levels during pregnancy were assessed on two consecutive days by measuring diurnal salivary cortisol at awakening, 30 minutes after awakening and 8 pm.

In order to obtain saliva, participants were provided with six appropriately-labelled conical tubes (salivettes®) containing oral swabs for saliva collection, and instructed on how to take the samples.

6.3.3 Procedures

Upon recruitment to the study, maternal ED diagnosis and other psychiatric diagnosis were determined using the DSM-IV in order to determine eligibility and group allocation.

Maternal assessments

Following recruitment to the study participants were invited to take part in two assessments during pregnancy:

1. *Mid-pregnancy assessment:* This assessment took place at 18 weeks gestation (sd. 4.1). There was no difference in the time of completion of mid-pregnancy assessments between the three maternal groups: current ED group (19.3 weeks), recovered ED group (18.8 weeks) and healthy control group (17.5 weeks). At this assessment participants were asked to complete the: EDE-Q, BDI, STAI, PRAQ-R and PSS.

2. *Late pregnancy assessment:* Follow up assessment took place in late pregnancy at a mean of 33.2 weeks gestation (s.d. 1.5). There was no difference in the time of completion of follow up assessment between the current (33.5 weeks), recovered (33.3 weeks) and healthy control group (33 weeks). During this assessment participants completed the: EDE-Q, BDI, STAI, PRAQ-R and PSS questionnaires.

Salivary cortisol

During pregnancy, participants were asked to collect saliva samples at home for salivary cortisol at mid- and late pregnancy. At these time points, salivary cortisol concentrations were measured on three occasions throughout the day (on awakening, 30 minutes following awakening and 8pm), on two consecutive days. Detailed written instructions were given to participants and provided verbally by the researcher. See Chapter 2 (section 2.5.4) for full details of the procedures. Once participants had completed the saliva swabs they were returned by post to the research centre and analysed for cortisol (see section 2.5.4 of Chapter 2 for full details of cortisol analysis).

Attrition

Of the 88 participants, 83 (94.3%) participants completed questionnaires on maternal psychopathology in mid- pregnancy, and 72 (81.8%) participants completed a late pregnancy follow up assessment. Sixty-eight (77.3%) participants completed both mid- and late pregnancy assessments. In cases of missing data due to partial responses on maternal questionnaires, subscale or scale scores from maternal questionnaires were prorated if fewer than15% of items in each scale or sub-scale were missing.

Valid salivary cortisol measurements at mid-gestation were available on 52 (59.1%) participants and at late gestation valid salivary cortisol measures were available on 56 participants (63.6%). At mid-gestation women in the healthy control group were more likely than women in the current ED group to complete saliva samples (coefficient=1.3, 95% CI = .22- 2.35, p=0.017) and were more likely not to be in current employment (OR= 0.12, 95% CI = .046- .34, p<0.001). Maternal age, ethnicity, education and marital status at the mid-gestation assessment did not predict attrition. At late gestation women completing saliva samples were more likely to be employed (OR= 0.37, 95% CI = .15- .95, p=0.038) and were slightly older ($F(1, 86)=4.6$, p=0.034). No selective attrition was apparent in terms of maternal ED group in late gestation, furthermore marital status and ethnicity did not predict attrition at the late gestation assessment.

For the purpose of this investigation, two frequently used measures of HPA axis functioning were calculated: cortisol awakening response (CAR) and cortisol decline (Ice & James, 2007). The CAR represents the natural increase in cortisol in response to wakening, and is a delta score calculated by subtracting cortisol levels at awakening from cortisol levels 30 minutes following awakening. The CAR is thought to be a marker of subtle changes in HPA axis activity, and associations between the CAR during pregnancy and birth outcomes are increasingly being investigated (Huizink, Mulder, Robles de Medina, et al., 2004).

Since cortisol levels are at their peak in the morning, it has been postulated that it would take a major life event to elevate these levels further during pregnancy, evening cortisol levels may therefore be more sensitive to stress during pregnancy (Obel, et al., 2005). High evening cortisol levels are reflective of less recovery from high morning cortisol levels, and smaller cortisol declines throughout the day are thought to reflect cortisol dysregulation. Therefore, a second measure of HPA axis functioning during pregnancy, 'cortisol decline', was calculated by subtracting evening cortisol levels from cortisol levels on wakening.

Statistical methods

Initial analyses was undertaken to investigate the characteristics of the data and to check the underlying assumptions of the statistical tests. Logarithm transformations were applied to skewed data when appropriate, and the transformed variables were used in the main analyses. Repeated measures ANOVA were used to investigate differences in ED symptoms, depression, state anxiety and trait anxiety during mid and late gestation, between the maternal groups. Pregnancy assessment time was used as the within subjects factor and maternal group was as a between subjects factor. Effect sizes for main effects were calculated using partial eta squared (η^2).

Group differences were followed up with Bonferroni tests, in order to account for multiple comparisons. Paired t-tests were used to examine the within group changes in maternal psychopathology across pregnancy. Significant main effects were explored using ANCOVA, confounders included in these analyses were maternal age, ethnicity and parity. Where appropriate the potential mediating effects of pre-pregnancy BMI and other psychiatric history were explored.

After log-transformation of salivary cortisol levels, linear regression analysis was used to assess differences between maternal groups in cortisol levels at: awakening, awakening + 30 and 8pm, CAR and cortisol decline. Unadjusted models were initially run (controlling for time of wakening and gestation in weeks), and were then adjusted for confounding variables (maternal age, ethnicity, parity, pregnancy smoking and other psychiatric history). Associations between measures of psychopathology during pregnancy and salivary cortisol were investigated using linear regression and multiple linear regression models.

6.4 Results

6.4.1 Socio-demographic data

Table 6.1 shows the demographic characteristics of the core sample by maternal group. The majority of women in the sample were of white ethnicity, were married or cohabiting, had no previous children and completed A-levels or higher education. Women in the current ED group were slightly younger (mean age 28.3; coefficient= -0.38, 95% CI = -6.4/-1.1, p=0.006) and less likely to be multiparous compared to women in the healthy control group (coefficient=0.3, 95% CI 0.1/1.1, p=0.07).

Mean pre-pregnancy BMI were 22.9 (s.d. 5.2), 21.8 (s.d. 5.1) and 23.9 kg/m^2 (s.d. 5.2) in the current ED, recovered ED and healthy control group respectively. BMI ranged from 13.8 to 30.5 kg/m^2 in the current group, 19.6-43.5 kg/m^2 in the past ED group, and 18.6-34.1 kg/m^2 in the healthy control group.

During pregnancy, 13 (48.1%) women in the current ED group were receiving regular psychological treatment at specialist ED outpatient services, 1 women was being treated as an inpatient on an ED ward and 4 (14.8%) women were engaged in on-line treatment for BN.

Table 6.1: Socio-demographic characteristics of the core NEST-p sample by maternal eating disorder group

	Current N=27	Recovered N=26	Healthy Control N=35
Maternal age: mean(s.d)	*28.3(5.6)*	*31.7(5.4)*	*32.1(4.9)*
Coefficient (95% CI), p value	*-0.4 (-6.4/-1.1) p=0.006*	*-0.4 (-3.1/2.3) p=0.77*	*Ref*
Pre-Pregnancy BMI: mean(s.d)	*22.9 (5.2)*	*21.8 (5.1)*	*23.9(3.4)*
Coefficient (95% CI), p value	*-1.1 (-3.5/ 1.3) p=0.35*	*0.9 (-1.3/ 3.3) p=0.44*	*Ref*
Gestational Weight Gain (kg): mean (s.d)	*11.5 (3.8)*	*10.6 (4.9)*	*10.3 (4.5)*
Coefficient (95% CI), p value	*1.2 (-1.8/4.1) p=0.43*	*0.3 (-2.5/3.1) p=0.83*	*Ref*
Married/Cohabiting: n(%)	21 (77.7)	20 (76.9)	31 (88.5)
OR (95% CI), p value	2.2 (0.5/8.8) p=0.25	2.3 (0.5/9.2) p=0.23	Ref
White ethnicity: n(%)	20 (74.1)	23 (88.5)	29 (82.7)
OR (95% CI), p value	1.6 (0.49/5.7) p=0.40	0.6 (0.14/2.8) p= 0.54	Ref
Multiparity: n(%)	6 (22.2)	8 (30)	15 (44.1)
OR (95% CI), p value	0.3 (0.1/1.1) p=0.07	0.5 (0.1/1.6) p=0.29	Ref
Education: A-Levels/Higher: n(%)	23 (85.1)	18 (78.2)	27 (79.4)
OR (95% CI), p value	0.6 (0.1/2.5) p=0.56	1.1 (0.2/3.9) p=0.91	Ref
Pregnancy smoking: n(%)	5 (18.5)	3 (13.0)	1 (2.8)
OR (95% CI), p value	7.7 (0.8/70.6) p=0.07	5.1 (0.4/52.3) p=0.17	Ref

Comparisons based on linear regression (in italics) and logistic regression, Ref = unexposed reference group.

6.4.2 Maternal psychopathology

Eating Disorder Examination Questionnaire

Results of the ANOVA indicated that EDE-Q scores during pregnancy were significantly different between the maternal groups ($F(1,61)=41.8$, $p<0.001$, $\eta^2=0.29$). As shown in Table 6.3, multiple comparisons (with bonferroni correction) indicated that EDE-Q scores were higher in the current ED group compared to both the recovered ED (mean difference=1.5, 95% CI=0.8/2.4, $p<0.001$) and healthy control (mean difference=2.5, 95% CI=1.8/3.1), $p<0.001$) groups. Scores on the EDE-Q were also higher in the recovered ED group compared to the healthy control group (mean difference=0.9, 95% CI=0.3/1.5), $p=0.001$).

Global EDE-Q scores were found to reduce during pregnancy ($F(1, 61) = 22.59$, $p<0.001$, $\eta^2=0.27$). Additionally, a significant interaction of maternal group and assessment time ($F(2, 61) =12.7$, $p<0.001$, $\eta^2=0.58$) was found. As shown in Figure 6.1 EDE-Q scores were found to significantly decreased across pregnancy in the current ED group ($t(15)=3.6$, $p=0.002$); but remained stable in the recovered ED ($t(20)=1.5$, $p=0.15$) and healthy control groups ($t(26)= -2.7$, $p=0.78$), Table 6.3.

To explore the differences, significant effects were followed up with an ANCOVA. After adjusting for confounders (maternal age, ethnicity, parity), the main effect of assessment time on EDE-Q scores reduced ($F(1, 55) = 2.18$, $p=0.64$, $\eta^2=0.003$). Group differences ($F(1, 55) = 20.08$, $p<0.001$, $\eta^2=0.42$) and interaction effects ($F(2, 55) = 8.22$, $p<0.001$, $\eta^2=0.23$) persisted with large effect sizes. Table 6.2 displays the frequency of eating disorder behaviours during mid- and late pregnancy across maternal ED groups.

The majority of women in the current ED group reported objective (76.4%) or subjective (82.3%) binge eating during mid-pregnancy, compared to 38.1% and 19.0% of women reporting objective or subjective binge eating, respectively, in the recovered ED group. The number of women reporting binge eating reduced in late pregnancy, and 41.2% of women in the current group reported an episode of objective binge eating in the past 28 days, compared to 19.0% in the recovered ED group and 10.3% in the healthy control group. Subjective binge eating also reduced to 47% in the current ED group and 9.5% in the recovered ED group. In late pregnancy no women in the healthy control group reported an episode of subjective binge eating.

Only women in the current ED group reported an episode of self-induced vomiting (SIV) in mid-pregnancy (29.4%), which remained relatively stable in late gestation (23.5%). However, the frequency of SIV within this group decreased significantly across gestation from a mean of 10.5 (s.d 11.1) times to 6.2 (s.d. 2.8) times in the previous four weeks. Laxative and diuretic use was absent during pregnancy in all three groups of participants, Table 6.2

Twenty-three per-cent of women in the current ED group reported an episode of excessive exercise in mid-pregnancy, which was absent in this group in late pregnancy. Excessive exercising was relatively uncommon during pregnancy in the remaining sample, in both early and late pregnancy, Table 6.2.

Table 6.2: Frequency n (%) of eating disorder behaviours during mid- and late pregnancy by eating disorder group

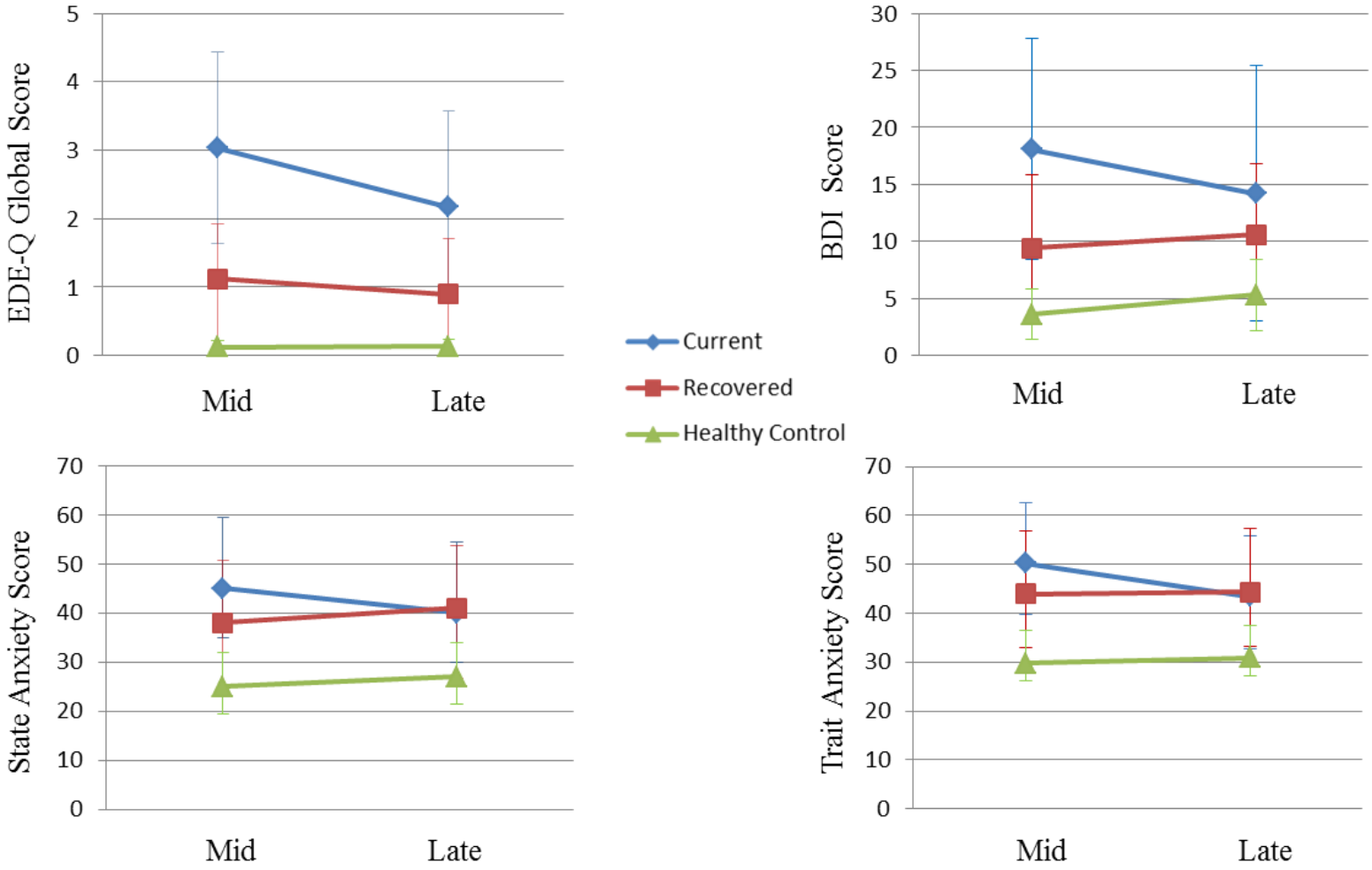
	Mid-pregnancy			***Late Pregnancy***		
	Current n=17	Recovered n=21	Healthy Control n=29	Current n=17	Recovered n=21	Healthy Control n=29
Objective binge eating	13 (76.4)	8 (38.1)	7 (24.1)	7 (41.2)	4 (19.0)	3 (10.3)
Subjective binge eating	14 (82.3)	4 (19.0)	1 (3.4)	8 (47.1)	2 (9.5)	0
SIV	5 (29.4)	0	0	4 (23.5)	0	0
Laxative Use	0	0	0	0	0	0
Diuretic Use	0	0	0	0	0	0
Excessive exercise	4 (23.5)	1 (4.7)	1 (3.4)	0	1 (4.7)	0

Table 6.3: Maternal psychopathology during mid- and late pregnancy by maternal group

	Current n=17		Recovered n=21		Healthy Control n=29		Group Differences p value
gestation	***mid***	***late***	***mid***	***late***	***mid***	***late***	
EDE-Q	3.0 (1.3)	2.2 (1.5)*	1.0 (0.8)	0.9 (0.9)	0.3 (0.5)	0.1 (0.2)	CED vs. HC: p<0.001 RED vs. HC: p=0.001 CED vs. RED: p<0.001
Restraint	2.2 (1.8)	1.4 (1.5)	0.8 (0.8)	0.5 (0.6)	0.2 (0.5)	1.3 (0.4)	
Weight concern	3.4 (1.4)	2.9 (1.8)*	1.3 (1.1)	1.3 (1.3)	0.3 (0.7)	0.1 (0.3)	
Shape concern	3.9 (1.6)	3.0 (1.8)*	1.5 (1.3)	1.4 (1.5)	0.4 (0.7)	0.2 (0.2)	
Eating concern	2.5 (1.4)	1.7 (1.5)*	0.8 (0.8)	0.4 (0.8)	0.08 (0.2)	0.05 (0.1)	
BDI	17.6 (9.9)	15.0 (10.4)	8.9 (6.2)	12.4 (8.5)	3.8 (2.5)	5.2 (3.1)*	CED vs. HC: p<0.001 RED vs. HC: p=0.013 CED vs. RED: p=0.01
STAI-State	45.3 (15.1)	42.3 (10.3)	38.2 (12.7)	41.8 (14.5)	26.4 (7.9)	27.8 (5.5)	CED vs. HC: p<0.001 RED vs. HC: p=.013 CED vs. RED: p=0.65
STAI-Trait	49.6 (12.4)	46.0 (11.4)*	43.5 (13.3)	43.9 (11.8)	29 (6.7)	30.9 (3.6)	CED vs. HC: p<0.001 RED vs. HC: p<0.001 CED vs. RED: p=0.64
PRA	33.3 (10.3)	32.1 (9.4)	26.6 (8.2)	27.3 (8.3)	18.9 (5.3)	20.3 (6.7)	CED vs. HC: p<0.001 RED vs. HC: p=0.013 CED vs. RED: p=0.11
Handicapped child	3.7 (1.8)	2.7 (1.8)	2.6 (1.1)	2.7 (1.1)	2.1 (0.7)	2.5 (0.8)	
Appearance	4.2 (1.1)	4.0 (1.2)	2.9 (1.1)	3.0 (1.1)	1.6 (0.5)	1.7 (0.8)	
Child birth	3.2 (1.1)	2.7 (1.5)*	3.3 (1.5)	3.3 (1.7)	2.3 (1.0)	2.1 (0.9)	
PSS	20.7 (6.4)	21.0 (5.4)	18.0 (7.1)	19.1 (7.2)	13.2 (4.4)	12.6 (4.6)	CED vs. HC: p<0.001 RED vs. HC: p<0.001 CED vs. RED: p=0.331

**p<0.001 *p<0.01: within group differences based on paired t-test; CED=current ED group; RED=recovered ED group; HC= Healthy control group, Between group differences based on post-hoc repeated measures ANOVA with bonferroni correction applied

Figure 6.1: Maternal psychopathology in mid- and late pregnancy, by maternal group



Becks Depression Index

BDI scores in pregnancy were significantly different between maternal groups ($F(1,56) = 20.2$, $p<0.001$, $\eta^2=0.41$), and were higher in the current ED group compared to the recovered ED group (mean difference=6.1, 95% CI=1.1/11.4, p=0.012) and the healthy control group (mean difference=11.6, 95% CI=7.1/16.1, p<0.001). BDI scores in pregnancy were also higher in the recovered ED group compared to the healthy control group (mean difference=5.4, 95% CI=0.9/10.1, p<0.015). Main effects of assessment time on BDI score were not present ($F(1, 56) = 0.15$, $p=0.69$, $\eta^2=0.003$). However, a significant interaction between maternal group and assessment time ($F(2, 56) = 4.13$, $p<0.021$, $\eta^2=0.58$), was found. Eta squared results from this analysis were indicative of large effect sizes. As shown in Figure 6.1, BDI scores increased across pregnancy in the healthy control group ($t(25)= 1.7$, $p=0.002$, $p=0.001$), but did not significantly change in the current ($t(16)= -3.6$, $p=0.17$) or recovered ED groups ($t(20)=1.2$, $p=0.28$), see Table 6.3for post-hoc comparisons.

Findings from an ANCOVA (controlling for maternal age, ethnicity and parity) revealed that group differences on BDI scores in pregnancy ($F(1, 55) = 4.47$, $p<0.016$, $\eta^2=0.13$) persisted with reduced effect. Interaction effects of maternal group and assessment time were no longer present when covariates were included in the model ($F(2, 55) = 0.66$, $p<0.79$, $\eta^2=0.001$).

State-Trait Anxiety Inventory

State anxiety scores on the STAI did not change during pregnancy ($F(1, 64) = 0.15$, $p=0.70$, $\eta^2=0.002$), but were different between the maternal groups ($F(1,64) = 20.2$, $p<0.001$, $\eta^2=0.38$). Higher state anxiety scores were observed in the current (mean difference=16.4, 95% CI=9.2/23.5, p<0.001) and recovered (mean difference=13.6, 95% CI=6.8/20.3, p<0.001) ED groups, compared to the healthy control group; state anxiety scores were found to be comparable between the two ED groups (mean difference=2.8, 95% CI= -4.8/10.4, p=1.0).

Furthermore, there was a significant interaction of maternal group and assessment time ($F(2, 64) =4.17$, $p<0.020$, $\eta^2=0.12$). As shown in Figure 6.1, state anxiety scores reduced in the current group over time and increased in both the recovered and healthy control group, further post hoc tests revealed that these differences were not significant, Table 6.3. After including covariates in the model the main effects of maternal ED

group remained ($F(1,58) = 14.2$, $p<0.001$, $\eta^2=0.32$) with a large effect size, group by time interactions were no longer significant ($F(2,58) = 1.72$, $p=0.18$, $\eta^2=0.012$).

Similarly, trait anxiety scores on the STAI remained stable during pregnancy ($F(1, 63) = 5.5$, $p=0.36$, $\eta2=0.068$). There was a main effect of maternal group on trait anxiety scores over time ($F(1,63) = 21.3$, $p<0.001$, $\eta2=0.40$), and significant interaction of group and assessment time ($F(2, 63) = 9.19$, $p<0.001$, $\eta2=0.26$). As shown in Figure 6.1, STAI trait scores reduced in the current ED group over time ($t(16)= -3.6$, $p=0.003$) and remained relatively stable in both the recovered ED group ($t(25)= -0.5$, $p=0.67$) and healthy control group ($t(27)= 1.2$, $p=0.09$), Table 6.3. After including covariates in the model the main effects of maternal ED group ($F(1,60) = 16.4$, $p<0.001$, $\eta2=0.35$) and group by time interactions ($F(2,60) = 4.78$, $p=0.012$, $\eta2=0.14$) persisted.

Pregnancy Related Anxiety and Perceived Stress

In mid-pregnancy PRA was found to be higher in the current (mean 33.3, s.d. 13.3) and recovered (mean 26.6, s.d. 8.2) ED groups, compared to the healthy control group (mean 18.9, s.d. 5.3). PRA scores decreased slightly by pregnancy in all three maternal groups, these differences was not significant after Bonferroni adjustment for multiple testing, Table 6.3.

In mid-gestation perceived stress was also high in both the current (mean 20.7, s.d. 6.4) and recovered ED groups (mean 18.0, s.d. 7.1), compared to the healthy control group (mean 13.2, s.d. 4.4). PSS scores had reduced in late gestation in all groups, but this reduction was not significant after adjustment for multiple testing.

Due to sample size it was not possible to statistically test any differences in psychopathology during pregnancy between ED diagnostic categories. However, exploratory analyses suggested EDE-Q scores were slightly higher in women with BED compared to women with AN or BN. On the other hand state and trait anxiety during pregnancy was higher in women with AN and BN compared to women with BED, see Table 6.4.

Table 6.4: Maternal psychopathology by eating disorder classification in mid-pregnancy

Psychopathology	AN Type n=13	BN Type n=6	BED Type n=4
EDE-Q	2.9 (1.3)	2.8 (1.5)	3.6 (1.1)
BDI	17.7 (8.7)	19.7 (13.2)	13.7 (7.2)
STAI State	45.8 (15.4)	49.3 (16.5)	37.5 (12.1)
STAI Trait	50.4 (11.8)	53.6 (14.6)	40.5 (7.7)

6.4.3 Maternal cortisol levels in pregnancy

Mid-pregnancy saliva samples were completed at a mean of 26.3 weeks gestation, the gestation that the samples were taken was comparable across the three maternal groups: current ED group (25.8 weeks), recovered ED group (26.2 weeks) and healthy control group (26.5 weeks). Late pregnancy saliva samples were completed at a mean of 33.5 weeks gestation, with no differences in timing between the maternal groups: current ED group (33 weeks), recovered ED group (33.1 weeks) and healthy control group (33.5 weeks).

Correlation analysis was used to assess the relationship between samples taken on day one and day two during pregnancy. Results of these analyses indicated strong correlations between the two sampling days in mid-pregnancy: awakening ($r=0.60$, $p<0.001$), 30 minutes after awakening ($r=0.58$, $p<0.001$) and at 8 pm ($r=0.66$, $p<0.001$). In late pregnanacy, correlations between the two sampling days were also strong on awakening ($r=0.52$, $p<0.001$), 30 minutes after awakening ($r=0.55$, $p<0.001$) and at 8pm ($r=0.56$, $p<0.001$. Therefore, mean values over the two days were used in the main analyses.

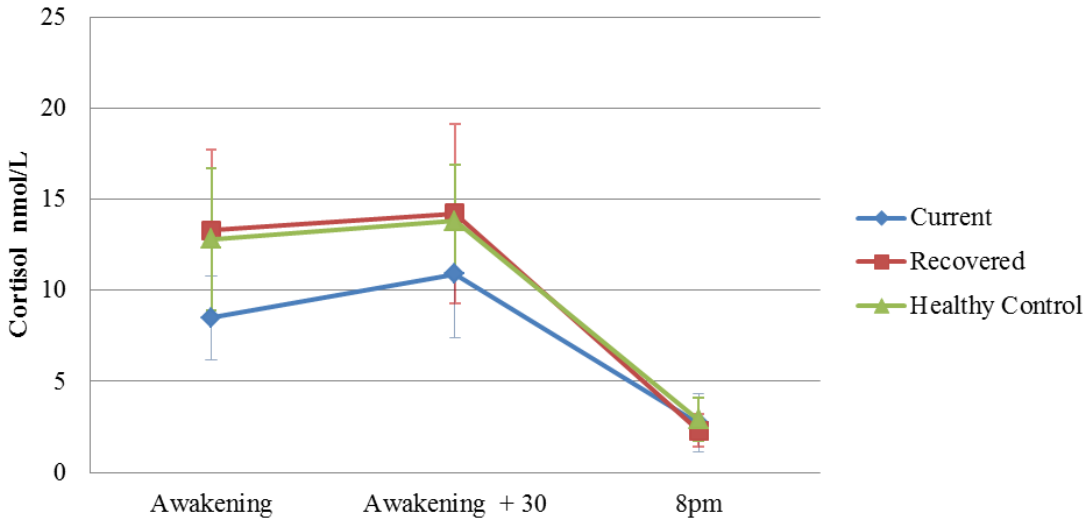
In mid-pregnancy median morning cortisol levels were: 11.9 nmol/L (IQR = 9.3 – 14.6) 5.0) on awakening, 13.0 nmol/L (IQR = 10.5 – 16.3) 30 minutes later and 2.3 nmol/L (IQR 1.8 – 3.4) in the evening. Later in pregnancy medians values were: 11.1 nmol/L (IQR = 8.8 – 14.3) on awakening, 12.1 nmol/L (IQR = 10.0 – 15.3) 30 minutes later and 3.2 nmol/L (IQR = 0.7 – 3.2) in the evening. As expected, evening cortisol levels increased between mid and late pregnancy ($t(38) = 3.8$, $p<0.001$), however no

differences were observed between the two assessment points on awakening (t(39) = -3.1, p=0.76), or 30 minutes after awakening (t(38) = 0.8, p=0.63).

Mid-pregnancy

Figure 6.2 illustrates cortisol levels in mid-pregnancy by maternal group. Cortisol levels on awakening were lower in the current group (9.3 nmo/L, IQR 6.5 – 9.3) compared to the healthy control group (12.8 nmo/L, IQR 9.5 – 15.9) and recovered group (13.2 nmo/L, IQR 17.8 – 14.8), and remained lower 30 minutes after awakening. Evening samples were comparable across the three groups.

Figure 6.2: Salivary cortisol levels (nmol/L) by maternal eating disorder group in mid-pregnancy



Linear regression of salivary cortisol (controlling for time of wakening and gestation) in mid-pregnancy indicated that women in the current group had significantly lower cortisol levels at awakening (coefficient-0.40, 95% CI = -0.66/-0.14, p=0.003) and 30 minutes after awakening (coefficient -0.23, 95 % CI=-0.57/-0.009, p=0.043), compared to the healthy control group. After adjusting for confounding variables (maternal age, ethnicity and parity) these differences persisted for the wakening cortisol sample, but not 30 minutes following wakening. Table 6.5. Including pregnancy smoking and psychiatric history in the model made only a small difference to these findings.

In both unadjusted and adjusted analyses evening cortisol levels in the current (adjusted coefficient-0.51, 95% CI=-1.59/0.57, p=0.34) and recovered ED groups (adjusted coefficient-0.70, 95% CI=-1.57/-1.70, p=0.11), were comparable to evening cortisol levels in the healthy control group, see Table 6.5. The decline in cortisol throughout the

day was found to be significantly lower in the current ED group (coefficient=-4.1, 95% CI= -7.2/-0.9, p=0.01), compared to the healthy control group. Values in the recovered ED group were comparable to the healthy control group (coefficient= 1.0, 95% CI= -1.6/3.6, p=0.5). This pattern persisted in adjusted analyses, see Table 6.5.

Late pregnancy

Figure 6.3 illustrates cortisol levels in late-pregnancy by maternal group. Later in pregnancy, cortisol levels (controlling for time of wakening and gestation) remained lower on awakening in the current ED group (coefficient-0.24, 95% CI= -0.46/-0.009, p=0.042), compared to the healthy control group, some attenuation was observed after adjusting for confounding variables (coefficient-0.23, 95% CI= -0.51/0.03, p=0.079). In both unadjusted and adjusted analysis no differences were observed in cortisol levels at 30 minutes after awakening or evening cortisol levels in the current or recovered ED groups compared to the healthy control group, Table 6.6.

In late pregnancy cortisol decline throughout the day remained lower in the current ED groups compared to the healthy control group, see Table 6.6. Including pregnancy smoking and psychiatric history in the model made only a small difference to these findings.

Figure 6.3: Salivary cortisol levels (nmol/L) by maternal eating disorder group in late pregnancy

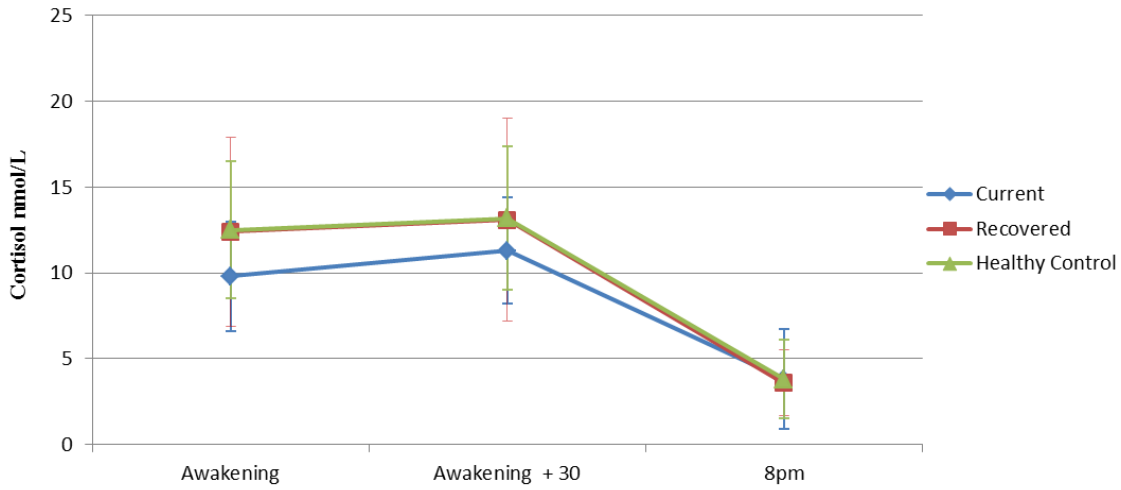


Table 6.5: Linear regression of log-transformed maternal salivary cortisol in mid-pregnancy by eating disorder group

	Unadjusted [1]			**Adjusted [2]**		
	Current n=10	**Recovered n=18**	**Healthy Control n=24**	**Current n=10**	**Recovered n=18**	**Healthy Control n=24**
Awakening: Mean/Median	8.5/9.3	13.2/13.4	12.8/12.6			
coefficient (95% CI),	**-0.40**	0.03		**-0.23**	-0.10	*Ref*
p value	**(-0.66/-0.14)**	(-0.28/0.14)	*Ref*	**(-0.57/-0.009)**	(-0.12/0.009)	
	p=0.003	p=0.81		**p=0.043**	p=0.36	
Awakening + 30 Minutes: Mean/Median	10.9/9.4	14.1/13.5	13.7/13.4			
coefficient (95% CI),	**-0.24**	0.006		-0.13	0.09	*Ref*
p value	**(-0.47/-0.009)**	(-0.18/-0.19)	*Ref*	(-0.37/0.10)	(-0.10/0.28)	
	p=0.041	p=0.94		p=0.25	p=0.34	
8pm: Mean/Median	2.6/2.1	2.3/1.9	2.9/2 .7			*Ref*
coefficient (95% CI),	-0.25	-0.60		-0.51	-0.70	
p value	(-1.20/0.69)	(-1.38/0.18)	*Ref*	(-1.59/0.57)	(-1.57/-1.70)	
	p=0.59	p=0.13		p=0.34	p=0.11	
CAR : Mean/Median	0.9/1.3	2.4/1.7	0.9/0.2			
coefficient (95% CI),	1.6	-0.93		2.2	-1.1	*Ref*
p value	(-1.19/4.47)	(-3.5/1.71)	*Ref*	(-1.01/5.33)	(-3.81/1.61)	
	p=0.26	p=0.48		p=0.17	p=0.41	
Cortisol Decline: Mean/Median	5.8/6.7	10.95/10.2	*9.9/7.19*			
coefficient (95% CI),	**-4.07**	1.00		**-6.72**	0.49	*Ref*
p value	**(-7.18/-0.95)**	(-1.57/ 3.58)	*Ref*	**(-12.39/ -1.07)**	(-3.78/4.76)	
	p=0.011	0.438		**p=0.021**	p=0.81	

[1] controlling for time of wakening and gestation; [2] adjusting for maternal age, ethnicity and parity

Ref = unexposed reference group

Table 6.6: Linear regression of log-transformed maternal salivary cortisol in late pregnancy by eating disorder group

	Unadjusted [1]			**Adjusted [2]**		
	Current n=17	**Recovered n=15**	**Healthy Control n=25**	**Current n=17**	**Recovered n=15**	**Healthy Control n=25**
Awakening: Mean/Median	9.9/10.5	12.4/11.5	12.5/11.4			
coefficient (95% CI),	**-0.24**	-0.04		-0.23	0.06	*Ref*
p value	**(-0.46/-0.009)**	(-0.27/0.19)	*Ref*	(-0.51/0.03)	(-0.31/0.19)	
	p=0.042	p=0.73		p=0.079	p=0.63	
Awakening + 30 Minutes: Mean/Median	11.0/11.1	14.4/11.6	12.1/12.9			
coefficient (95% CI),	-0.16	0.04		-0.15	0.009	*Ref*
p value	(-0.40/0.081)	(-0.21/0.29)	*Ref*	(-0.43/0.12)	(-0.25/0.27)	
	p=0.19	p=0.73		p=0.26	p=0.94	
8pm: Mean/Median	2.7/2.6	3.6/2.9	2.8/3.4			
coefficient (95% CI),	-0.25	-0.60		-0.51	-0.70	*Ref*
p value	(-1.20/0.69)	(-1.38/0.18)	*Ref*	(-1.59/0.57)	(-1.57/-1.70)	
	p=0.59	p=0.13		p=0.34	p=0.11	
CAR	1.1/0.5	2.4/1.5	0.6/0.3			
coefficient (95% CI),	0.09	2.18		0.40	1.79	*Ref*
p value	(-2.41/4.63)	(-0.83/5.20)	*Ref*	(-3.46/4.26)	(-1.60/5.21)	
	p=0.57	p=0.15		p=0.83	p=0.15	
Cortisol Decline	8.7/8.4	6.1/7.2	8.4/7.9			
coefficient (95% CI),	-3.11	-0.33		**-7.15**	-2.23	*Ref*
p value	(-6.36/0.13)	(-3.49/3.42)	*Ref*	**(-12.47/-1.84)**	(-6.96/2.50)	
	p=0.060	p=0.98		**p=0.010**	p=0.34	

[1] controlling for time of wakening and gestation; [2] adjusting for maternal age, ethnicity and parity

Ref = unexposed reference group

6.4.4 Relationship between psychometric measures and cortisol in pregnancy

Since the strongest effects of maternal ED group on cortisol were found on wakening and cortisol decline throughout the day, and to restrict the number of variables used in multivariate analysis, the associations between psychometric measures of psychopathology during pregnancy were examined in relation to these two markers of HPA axis activity.

In mid-pregnancy high EDE-Q scores were found to be predictive of low morning cortisol levels (coefficient=-1.1, 95% CI= -1.9/-0.2, p=0.02). After controlling for confounding variables (smoking, age, ethnicity and maternal psychiatric history) these effects reduced (coefficient=-0.6, 95% CI= -1.4/0.2, p=0.15). There was only a weak relationship with cortisol on awakening and cortisol decline and scores of perceived stress and pregnancy related anxiety, see Table 6.7. Furthermore, no relationship with scores on the STAI and morning cortisol levels was observed in mid-pregnancy. Cortisol decline was not associated with any other measures of psychopathology during mid-pregnancy.

Later in pregnancy a weaker relationship between global EDE-Q scores and awakening cortisol was observed (coefficient=-0.44, 95% CI= -0.9/-0.05, p=0.08). Cortisol levels on awakening and throughout the day were not found to be associated with any other measures of stress, depression or anxiety in late pregnancy, Table 6.7.

Table 6.7: Linear regressions of maternal cortisol and psychopathology in mid- and late pregnancy

	Mid-pregnancy					
	EDE-Q	BDI	PSS	PRA	State Anxiety	Trait Anxiety
Wakening Cortisol:						
coefficient	**-1.1**	-4.5	-5.5	-6.3	-5.2	-6.5
95% CI	**-1.9/0.16**	-10.2/1.2	-11.4/0.50	-13.7/1.13	-16.3/5.8	-16.8/3.8
p value	**p=0.02**	p=0.12	p=0.072	p=0.095	p=0.34	p=0.21
Cortisol Decline:	-0.06	-0.16	-0.30	-6.3	-0.33	-0.22
coefficient	-0.1/0.01	-0.65/0.32	-11.4/0.50	-0.80/0.21	-0.91/0.23	-1.09/0.65
95% CI	p=0.10	p=0.51	p=0.072	p=0.23	p=0.28	p=0.61
p value						
	Late Pregnancy					
Wakening Cortisol:						
coefficient	-0.44	2.3	-1.1	-3.9	-0.4	-2.1
95% CI	-0.9/0.05	-1.8/7.3	-6.3/4.2	-9.6/1.7	-7.4/6.6	-8.7/4.5
p value	p=0.08	p=0.24	p=0.68	p=0.17	p=0.92	p=0.52
Cortisol Decline:	-0.007	-0.14	-0.05	-0.13	0.02	-0.07
coefficient	-0.08/0.67	-0.32/0.30	-4.9/0.38	-0.69/0.41	-0.71/0.69	-0.71/0.56
95% CI	p=0.84	p=0.54	p=0.79	p=0.61	p=0.95	p=0.82
p value						

Adjusted for time of wakening and gestation

6.5 Discussion

The overall aim of this study was to investigate changes in psychopathology during pregnancy in women with current and past ED. Associations between cortisol levels during pregnancy and maternal psychopathology were also examined.

6.5.1 Psychopathology in pregnancy

As hypothesised, this study found that, women with active ED during pregnancy experienced a decrease in ED symptoms between mid and late gestation. Nevertheless, in late gestation the ED cognitions of women with active ED remained comparable to the clinical cut-off point for global EDE-Q scores of 2.3 (Mond, et al., 2004). The number of women reporting objective and subjective binge eating was also high in mid-pregnancy in women with current and recovered ED. Although a reduction in the number of women binge eating observed during pregnancy, they remained high. In line with previous investigations (Micali, Treasure, et al., 2007b), laxative and diuretic use was uncommon during pregnancy in this sample, although over 20% of women with active ED during pregnancy continued to induce vomiting as a means of weight control.

These findings are in line with previous studies which have indicated a reduction of ED symptoms during pregnancy, and may be reflective of women attempting to reduce the potentially harmful effects of their ED on their developing foetus. It has therefore been suggested that pregnancy represents a period of increased motivation for women with ED, and may be an optimal time for psychological intervention (Micali, 2010). Nevertheless, EDE-Q scores remained high in women with active ED, as did the number of women inducing vomiting. Although SIV remained relatively common in women with active ED during pregnancy, the frequency of episodes reduced in late pregnancy. These findings are in line with studies of women with BN, who have reported that whilst the number of women abstaining from SIV during pregnancy remains relatively stable during pregnancy (Crow, Keel, Thuras, & Mitchell, 2004), the frequency of episodes decrease across gestation (Lacey & Smith, 1987; Morgan, et al., 1999c). Therefore, clinicians' working with women with ED during pregnancy should be aware that intensive support treatment will continue to be required during pregnancy, with the aim to alleviate ED symptoms, as well as to prevent relapse in the post-natal period.

As expected, levels of depression were also higher in women with active ED during pregnancy, and indicated borderline levels of clinical depression, only a slight reduction

was observed across pregnancy. In comparison, an increase in depression scores during pregnancy was found in the healthy control group, although scores remained within the threshold considered to be 'normal ups and downs' (Beck, 1979). Furthermore, high levels of anxiety and stress persisted across pregnancy in women past and ED during pregnancy.

Several studies have indicated that co-morbid depression and anxiety are common in women with ED (Hudson, et al., 2007), however very few studies have investigated the course of symptoms during pregnancy. Only one previous study exists, which also reported high levels of anxiety during pregnancy in women with past/active ED, particularly when combined with a past depressive disorder (Micali, et al., 2010). In the present investigation, anxiety levels during pregnancy for women with ED (past and current) remained above the clinical cut-off point (39/40) for clinically significant STAI scores (Knight, Waal-Manning, & Spears, 1983). Furthermore, levels of anxiety in women with lifetime ED in this sample were found to be higher than levels reported in both community and hospital samples during pregnancy (Gunning, et al., 2011).

Given the associations between elevated stress and anxiety during pregnancy and poor birth outcomes (e.g. Kramer, et al., 2009), as well as long-term implications for infant development (Glover & O'Connor, 2002), clinicians should be aware of this elevated risk and routinely screen and monitor anxiety in women with a history of an ED during pregnancy. The implications of increased psychopathology during pregnancy on birth outcomes and infant development in this sample will be explored further in the following chapter.

6.5.2 Cortisol levels in pregnancy

In this investigation, different patterns of circadian salivary cortisol were observed in women with active ED during pregnancy. Specifically, low morning cortisol levels and a flatter cortisol decline throughout the day were apparent in women with active ED during mid-pregnancy, compared to women who had recovered from an ED prior to pregnancy and women without ED.

ED are typically associated with hyperactivity of the HPA axis (Favaro, et al., 2008), therefore, the finding of low morning cortisol levels in the present investigation was surprising. However, few studies have examined circadian rhythms of salivary cortisol in women with ED, and no previous investigations have done so during pregnancy. The

difference could therefore in part be due to the characteristics of the sample or the methods employed in the present study. In order to gain a more in-depth understanding of HPA axis activity during pregnancy further investigation and replication of these findings in larger samples will be crucial.

A previous investigation of circadian salivary cortisol rhythms in a general population sample, found that high levels of ED related attitudes and behaviours (such as restraint, hunger, binge eating and body esteem) were negatively related to the CAR (Therrien, et al., 2008), indicating a blunting of HPA axis reactivity. Similarly, in this study low morning cortisol levels were associated with high EDE-Q scores, particularly in mid-gestation. It has been postulated that prolonged periods of hypercortisolism may result in a blunting or 'burn out' of the HPA axis (Heim, Ehlert, & Hellhammer, 2000). In this study, participants in the in the active ED group were predominantly drawn from specialist ED services and had long durations of elevated psychopathology, which may have resulted in reduced morning cortisol levels.

On the other hand, women in this study continued to demonstrate a significant cortisol response to wakening and flatter cortisol declines throughout the day, which is indicative of less recovery from high morning cortisol levels. It has previously been reported that flattened diurnal cortisol rhythm during pregnancy are associated with higher levels of stress and anxiety (Kivlighan, DiPietro, Costigan, & Laudenslager, 2008; Obel, et al., 2005).

Although there is strong evidence for associations between maternal psychopathology during pregnancy and adverse birth outcomes, evidence for cortisol as a mediator is inconsistent (O'Donnell, et al., 2009). Over-exposure to exogenous glucocorticoids has consistently been shown to have an adverse effect on foetal development (Sloboda, Challis, Moss, & Newnham, 2005), furthermore high levels of maternal CRH have been associated with a 3.3 increase risk of preterm birth (Wadhwa, et al., 2004). Comparatively, Diego (Diego, et al., 2006) found only modest associations between maternal urinary cortisol and birth weight.

Few studies have investigated the pattern of salivary cortisol throughout the day in relation maternal psychopathology and birth outcomes. Kivlighan and colleagues reported that high morning cortisol and steeper morning declines in salivary cortisol, were associated with smaller birth weights (Kivlighan, et al., 2008). Leading the authors to hypothesise that low morning cortisol and flattening of the diurnal rhythm throughout

the day may reduce the harmful effects of maternal stress hormones on foetal exposure (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Kivlighan, et al., 2008). Therefore, the patterns of diurnal salivary cortisol of women with active ED observed in the present investigation may serve a protective function against adverse birth outcomes.

Based on previous literature it was hypothesised that cortisol levels in pregnancy would be predicted by high levels of maternal psychopathology and stress (Sandman, et al., 2011). Some modest relationships were observed between perceived stress and pregnancy related anxiety, and cortisol levels during pregnancy in this sample, and it is possible that given the small sample size in this study it may have lacked power to detect differences. However, the relationship between psychological and physiological measures of stress is complicated and while some studies have found relationships between the two during pregnancy (Obel, et al., 2005; Wadhwa, Dunkel-Schetter, Chicz-DeMet, Porto, & Sandman, 1996), others have not (Sarkar, Bergman, Fisk, & Glover, 2006), leading O'donnell and colleagues (2009) to conclude that the relationship between pre-natal stress or anxiety and maternal HPA functioning during pregnancy may be weak.

6.5.3 Strengths and limitations

The main strength of this study is its uniqueness to investigate both psychological and physiological markers of maternal anxiety and stress during pregnancy in women with ED. Furthermore, the methodology utilised in the present investigation has a number of advantages over previous investigations in this area. The women were followed up prospectively, and extensive validated measures of maternal psychopathology were employed. Furthermore, ED classification and other psychiatric diagnoses were made on the basis of diagnostic interview.

The main limitation of this investigation is that the overall sample size and number of women in each group was small. Therefore this study may have lacked the power to detect potential differences. Furthermore, some differences in outcomes existed between different ED types; however, due to small sample size it was not possible to formally test these differences. Women with ED in this investigation were predominantly identified via specialist services, and may therefore represent a group of women with more severe psychiatric illness, and not be representative of women with ED in general.

In addition, the number of women not completing or returning their swabs was relatively high in this study and some selective attrition was apparent, which further reduced the sample and may have introduced bias into the results. Furthermore, only a single measure of HPA axis functioning was employed, diurnal salivary cortisol, and more extensive measures would strengthen the present investigation. Although salivary cortisol is a less invasive procedure for measuring cortisol compared to obtaining blood samples, high rates of attrition on salivary cortisol collection are problematic in research and future investigations should be aware of these difficulties and include procedures to improve saliva completion and return.

The length of time between the mid- and late pregnancy cortisol assessment was also relatively short. Typically a progressive increase in cortisol levels is observed between early and late pregnancy, in the present study only evening cortisol levels increased across gestation. Furthermore, it would be advantageous to have an early pregnancy or pre-pregnancy assessment in order to compare changes in psychopathology and cortisol levels before and during pregnancy. However, recruitment of pregnant samples, particularly women with ED is especially challenging, and identifying an appropriate sample prior to pregnancy, or earlier in gestation, may not have been possible. Additionally, several multiple comparisons were made throughout this investigation, which may have increased the risk of type I errors. Nevertheless, caution was made and corrections applied for the number of comparisons made within this study.

6.5.4 Conclusion and clinical implications

In conclusion, this study confirms and extends the findings of previous studies in this field of research. ED symptoms were found to reduce during pregnancy in women with active ED, but remained significantly elevated in late gestation. Furthermore, symptoms of anxiety and stress remained high in women with both active and remitted ED.

Given the potential harmful effects of elevated psychopathology during pregnancy on birth and infant outcomes, these findings further highlight the need for healthcare professionals to provide routine screening and treatment during pregnancy for women with both past and current ED. Treatment should not only focus on treating the ED, but should also be targeted at reducing co-morbid symptoms of anxiety. Clinicians should be aware of the increased risk for ante-natal depression and anxiety, not only for women with current ED but also women who have a past history of ED.

This is the first study to investigate cortisol levels during pregnancy in women with ED. Abnormal circadian rhythms were apparent in women with ED, with low cortisol levels on awakening and flatter cortisol declines across the day, replication of these findings in larger samples is required.

Chapter 7. Birth Outcomes and Infant Stress Regulation in Infants of Women with Eating Disorders

7.1 Introduction

7.1.1 Obstetric outcomes

As highlighted in previously, women with ED have been found to have an increased risk of obstetric complications (see sections 6.1.1 and section 1.5 of the Literature Review). Adverse birth outcomes, such as prematurity and low birth weight, have been associated with heath complications later in life, such as heart disease (Barker, 1990). Furthermore, obstetric complications have and have been identified as a risk factor for the development of psychological problems and have been implicated in the pathogenous of ED, (Cnattingius, et al., 1999; Favaro, et al., 2006; Lindberg & Hjern, 2003).

The potential underlying mechanisms for adverse birth outcomes in women with ED have not previously been investigated. As discussed in the literature review presented in Chapter 1, one possible pathway for obstetric complications in women with ED is via elevated levels of stress and co-morbid psychopathology during pregnancy (Micali & Treasure, 2009), resulting in high levels of glucocorticoids in foetal circulation. In the previous investigation, women with ED were found to experience high levels of stress and anxiety in both mid- and late pregnancy, as well as abnormal diurnal salivary cortisol rhythms (see Chapter 6). Therefore, it is important to investigate the potential implications of these findings on birth outcomes in women with ED.

7.1.2 Post-natal psychopathology

During the post-natal period women with ED have typically been found to experience a relapse of ED symptoms (Bulik, et al., 2007; Morgan, et al., 1999c; Stein & Fairburn, 1996; Welch, et al., 1997), as well as an increased risk of post-natal depression (Abraham, et al., 2001; Carter, et al., 2003; Mazzeo, et al., 2006; Morgan, et al., 2006). Only one study has investigated anxiety during the post-natal period in women with ED, which found high levels in women with both recent and past ED (Micali, et al., 2010).

7.1.3 Infant stress response

Maternal stress during pregnancy may alter the development of the foetal HPA axis, and in turn affect the infants' ability to respond appropriately to stressful situations in the

post-natal period (Davis, et al., 2011; Gutteling, et al., 2004; Gutteling, et al., 2005). Consequently, infants of women who experience elevated levels of pre-natal stress and anxiety may be vulnerable to psychological and behaviour problems during infancy. In support of this hypothesis, there is increasing evidence of an association between pre-natal exposure to anxiety and deficits in behavioural, emotional and cognitive development in their offspring (Glover, et al., 2009). Furthermore, there is also evidence that maternal stress or anxiety during pregnancy may have implications for future development of psychopathology such as schizophrenia, autism and attention deficit hyperactivity disorder (ADHD) (Glover, et al., 2009).

Given the high levels of anxiety and stress during pregnancy in women with ED identified in the previous chapter (section 6.4.2); infants of women with ED may be at risk for alterations in their stress response. Despite this, the stress response and cortisol levels have not been investigated in infants of women with ED.

7.2 Aims and hypotheses

The overall aim of this study was to examine obstetric complications and perinatal risk factors, e.g. maternal psychopathology, perceived stress and cortisol, for adverse birth outcomes in children of women with active and remitted ED. Additionally, differences in infants cortisol levels and response to a stressful situation were explored in infants of women with active and remitted ED, compared to a healthy control group. Specifically, this study aims to investigate:

1. changes in maternal ED psychopathology, depression, anxiety and stress between late gestation and 8 weeks post-natal, in women with active and remitted ED, compared to a healthy control group;

2. associations between psychological and physiological measures of stress (perceived stress and cortisol) and maternal psychopathology (ED, depression and anxiety symptoms) during pregnancy and birth weight and gestational age at delivery, in women with active and past ED, compared to a healthy control group;

3. infants' cortisol response to a stressful situation at eight weeks post-partum, in infants of women with active and remitted ED, compared to a healthy control group;

4. associations between infants' stress response (at 8 weeks post-partum) and psychological and physiological indicators of stress and maternal psychopathology during pregnancy and in the post-partum, in women with remitted and active ED, compared to a healthy control group.

Hypothesis under investigation

1. Women with a history of an ED will experience a recurrence of symptoms in the post-partum period

2. Maternal stress during pregnancy will predict a lower birth weight and shorter gestational length in babies in women with ED, compared to a healthy control group.

3. Infants of women with active and remitted ED during pregnancy will have an elevated stress response (cortisol) to a stress paradigm, compared to infants of women in a healthy control group.

4. Infant stress response will be related to maternal ED symptoms, anxiety and depression during pregnancy and post-natal psychopathology.

7.3 Methods

7.3.1 Participants

Of the 88 women who provided data during pregnancy, 76 women had delivered their babies. All but one pregnancy resulted in a live birth. Gestational age at delivery was available on 73 participants; there was some further attrition on participants' birth weight and mode of delivery, which was available on 66 participants.

A sub-sample of 59 (67%) mother and infant dyads, from the original 88 mothers recruited during pregnancy, whose infants were 8 weeks post-natal prior to September 2011 were followed up in the post-natal period. Fifteen (17%) participants had withdrawn from the study at this stage, one pregnancy (within the healthy control group) resulted in an elective abortion due to complications with the pregnancy, and ten (11.1%) infants had not reached the eight week assessment date by September 2011. Of the infants followed up at 8 week post-natal: 26 (29.5%) were male and 33 (37.5%) were female, at the time of assessment infant ages ranged from 6.7 to 12.8 weeks, with mean of 8.9 weeks. Full details of the methodology are outlined in Chapter 2.

Inclusion and exclusion criteria

Of the core sample of 88 women recruited during pregnancy all women who had delivered their babies or attended their infants 8 week immunisations by September 2011 were eligible for inclusion.

7.3.2 Materials and measures

Full details of the materials used and procedures followed in this investigation are outlined in section 2.5.4 of the General Aims and Methodology chapter.

Obstetric outcomes

For the purpose of this investigation, the following data was extracted from obstetric records at the delivering hospital: birth weight (grams), gestational age at delivery (weeks), head circumference (cm) and mode of delivery (vaginal, elective/emergency caesarean, ventouse and/or forceps).

Maternal psychopathology

At 8 weeks post-natal self-reported ED symptoms were assessed using the EDE-Q (Fairburn & Bèglin, 1994). Self-reported perceived stress, state and trait anxiety, were assessed using: PSS (Cohen, et al., 1983) and STAI (Spielberger, et al., 1983), respectively.

Full details of the measures used within this investigation, including validity and reliability, are described in full in the General Aims and Methodology chapter, section 2.4.3.

Infant cortisol

Infant saliva was collected at routine immunisations at 8 weeks post-natal. Sorbettes (eye sponges) were used for infant saliva collection. To ensure an adequate sample, two Sorbettes were used together and then are placed in one conical tube for centrifugation.

Full details of the laboratory analysis of infant salivary cortisol are provided in the methodology chapter General Aims and Methodology chapter, section 2.5.4.

7.3.3 Procedures

Birth outcomes: Participants were contacted around the time of their EDD and the date of birth of their baby recorded. Obstetric records were requested from maternity services and the details extracted from maternal scan notes and discharge summaries.

Eight week post-natal assessment: On the day of their infants eight week immunisations participants were visited at home and asked to complete the EDE-Q, BDI, STAI, and PSS questionnaires.

A researcher attended the eight week immunisations and recorded details of the sampling timings and completed a post-immunisation saliva swab with the infants 20 minutes following the immunisation, in order to measure their physiological response to stress. On the following day mothers were instructed to take samples from their infant at 8am and 8pm, following the procedures demonstrated by the researcher. Infant samples were stored by participants in their fridges, and returned by post to the research centre once all samples had been completed. Samples were frozen at 20°C until analysed. Record sheets were completed by participants, to include details of: time of wakening on both days, time of immunisations and exact timings of swabs, as well as details of any illness.

In order to assess infants' cortisol response to the immunisations a variable of 'stress response' was calculated by subtracting baseline levels from cortisol levels 20 minutes following the immunisations.

Statistical analyses

Initial analysis was undertaken to investigate the characteristics of the data and to check the underlying assumptions of the statistical tests. Linear and binary logistic regressions were used to investigate differences in obstetric outcomes across maternal groups. In order to investigate the relationship between maternal psychopathology and cortisol during pregnancy and main birth outcomes (length of gestation and birth weight) linear regression and multiple linear regressions were used.

Repeated measures ANOVA were used to investigate differences in ED symptoms, depression, state anxiety and trait anxiety between mid-gestation and 8 weeks post-natal, between the maternal groups. In these analyses, assessment time was used as the within subjects factor and maternal group as a between subjects factor. Effect sizes for main effects were calculated using partial eta squared ($\eta 2$).

Attrition

In order to examine the representative of the sample in the present investigation, the core sample of women who completed assessments during pregnancy were compared to

women with available obstetric data and the sub-sample of mother-infant dyads completing assessments at 8 week post-natal.

Of the women who had delivered their baby prior to this investigation there was no selective attrition across maternal groups, and the number of women with data on birth outcomes was similar in women with current ED (coefficient = -0.13, 95% CI = -0.32/0.06, p=0.16) and recovered ED (coefficient= -0.11, 95% CI=-0.29/0.08, p=0.29), compared to the healthy control group.

At 8 weeks post-natal the proportion of women in the current ED (n=18) and past ED (n=17) groups and healthy control group (n=24), were comparable to the core pregnancy sample. Furthermore, maternal age, ethnicity, marital status, parity, smoking in pregnancy was comparable in women who completed a post-natal follow-up and the core pregnancy sample. Women who were followed up 8 weeks post-natal had a slightly lower pre-pregnancy BMI (22.2 kg/m^2) compared to women who were not followed up (24.3 kg/m^2).

7.4 Results

7.4.1 Obstetric outcomes

Socio-demographic data

Table 7.1 shows the demographic characteristics of women with available obstetric information across maternal group. The majority of women in the sample were of white ethnicity, were married or cohabiting, had no previous children and completed A-levels or higher education. Women in the current ED group were younger (mean age 28.1; coefficient= -4.6, 95% CI = -3.7/-1.7, p=0.002) and less likely to be multiparous compared to women in the healthy control group (coefficient=0.3, 95% CI 0.06/1.1, p=0.06).

Table 7.1: Socio-demographic data of participants with obstetric data

	Current N=21	Recovered N=21	Healthy Control N=31
Maternal age: mean(s.d)	*28.1 (5.4)*	*31.7 (5.3)*	*32.7 (4.9)*
Coefficient (95% CI), p value	*-4.6 (-3.7/-1.7) p=0.004*	*-0.8 (-3.7/2.3) p=0.56*	*Ref*
Pre-Pregnancy BMI: mean(s.d)	*22.7 (3.9)*	*24.2 (5.6)*	*22.5(3.1)*
Coefficient (95% CI), p value	*-0.8 (-3.1/1.6) p=0.52*	*1.6 (-0.7/4.0) p=0.17*	*Ref*
Married/Cohabiting: n(%)	16 (76.2)	16 (76.2)	31 (90.3)
OR (95% CI), p value	2.9 (0.61/13.8) p=0.18	2.9 (0.61/13.8) p=0.18	Ref
White ethnicity: n(%)	14 (66.7)	16 (90.5)	26 (83.8)
OR (95% CI), p value	0.2 (0.03/1.2) p=0.075	0.4 (0.18/1.4) p=0.16	Ref
Multiparity: n(%)	3 (14.3)	6 (28.5)	12 (38.7)
OR (95% CI), p value	0.3 (0.06/1.1) p=0.06	0.6 (0.2/2.8) p=0.45	Ref
Education: A-Levels/Higher: n(%)	18 (85.7)	14 (77.8)	26 (86.7)
OR (95% CI), p value	1.1 (0.2/5.4) p=0.92	1.8 (0.4/8.5) p=0.42	Ref
Pregnancy smoking: n(%)	4 (19.1)	3 (16.7)	0 (0)

Ref=unexposed reference group

Birth outcomes

The mean birth weight of babies born to women with in the current ED group was 3,210g (1,800g-3,988) and 3,387g in women in the recovered ED group (2,390-3,988), compared to 3,367g (2,644-4,362) in the healthy control group. As shown in Table 7.2, results from regression analyses indicated that birth weights in the current ED group (coefficient = -117.4, 95% CI=-434.2/199.3, p=0.46) and recovered ED group (coefficient=58.8, 95% CI = 266.8/384.5, p=0.72) were comparable to birth weights in the healthy control group. The findings remained similar after adjusting for confounding variables, Table 7.2. The number of women with low birth weight deliveries (<2,500g) was slightly higher in the current ED group (9.5%) compared to the recovered ED group (5.3%) and healthy control group (4.0%), but this finding was not significant: coefficient=2.5, 95% CI=0.21/30.1, p=0.46.

Women in the current ED group had a mean gestational length of 39.1 weeks (33.6-41.7 weeks), compared to 40.2 weeks (38.4-32.3 weeks) in the recovered ED group and 39.7 (39.1-41.7) weeks healthy control group. Results of the analyses indicated that the length of gestation was similar in women with current ED during pregnancy (coefficient = 0.6, 95% CI = -1.5/0.31, p=0.18), and the recovered ED group (coefficient = 0.5, 95% CI = -0.39/1.4, p=0.25), compared to the healthy control group. After adjusting for confounding variables the length of gestation remained comparable in the three groups, see Table 7.2. The overall number of premature deliveries (<37 weeks) was low in this sample, and no women in the recovered ED group or healthy control group delivered prior to 37 weeks gestation, compared to 4 women (19.1%) in the current ED group.

The number of women requiring intervention during their pregnancy was 10 (34.5%) in the current group (6 caesarean section, and 4 ventouse/forceps), compared to 11 (37.9%) in the recovered ED group (4 caesarean section, and 5 ventouse/forceps), and 8 women (27.6%) in the healthy control group (4 caesarean section, and 3 ventouse/forceps). As shown in Table 7.2, there were no statistical differences in rates of intervention during delivery in the current (coefficient =2.0, 95% CI = 0.62/6.7, p=0.24) and recovered ED group (coefficient =3.1, 95% CI = 0.90/10.6, p=0.073), compared to the healthy control group, in both unadjusted and adjusted analyses.

Table 7.2: Linear and binary logistic regression of obstetric outcomes by maternal eating disorder groups

	Unadjusted			Adjusted [1]		
	Current	Recovered	Healthy Control	Current	Recovered	Healthy Control
Birth Weight (g) mean (s.d)	3,210 (595)	3,387 (482)	3,367 (493)			
coefficient (95% CI), p value	-117.4 (-434.2/199.3), p=0.46	58.8 (266.8/384.5), p=0.72	Ref	71.6 (-269.6/412.9), p=0.67	-117.4 (-259.4/409.2), p=0.65	Ref
Length of gestation (weeks) mean (s.d)	39.1(2.4)	40.2 (1.0)	39.7 (1.2)			
coefficient (95% CI), p value	-0.6 (-1.5/0.31), p=0.18	0.5 (-0.39/1.4), p=0.25	Ref	-0.6 (-1.6/0.44), p=0.25	-0.7 (-0.30/1.7), p=0.17	Ref
Head Circumference (cm) mean (s.d.)	33.9 (1.5)	34.8 (1.3)	34.1 (1.9)			
coefficient (95% CI), p value	-0.5 (-1.4/0.44), p=0.29	0.3 (-0.57/1.3), p=0.42	Ref	0.07 (-0.36/1.1), p=0.89	-0.5 (-1.1/1.0), p=0.92	Ref
Intervention during pregnancy: n (%)	10 (34.5)	11 (37.9)	8 (27.6)			
OR (95% CI) p value	2.0 (0.62/6.7), p=0.24	3.1 (0.90/10.6), p=0.073	Ref	1.7 (0.35/8.2), p=0.67	3.7 (0.65/21.7), p=0.14	Ref

[1] adjusted for maternal age, ethnicity, parity, smoking in pregnancy, child gender; Ref = unexposed reference group

Due to insufficient numbers of women in each group, it was not possible to formally test the difference between current ED sub-types during pregnancy, however, as shown in Table 7.3, birth weight was lower in women with current AN and higher in women with BED. Length of gestation, head circumference and the frequency of intervention during pregnancy were broadly similar across the ED categories.

Table 7.3: Obstetric outcomes by maternal eating disorder sub-type in pregnancy

	AN Type	BN Type	BED Type
length of gestation (weeks)	38.1 (2.7)	39.7 (1.9)	38.1 (40.6)
birth weight (g)	3,136 (713)	3,256 (612)	3,317 (215)
head circumference (cm)	34.8 (1.0)	33.3 (1.7)	33.0 (1.0)
Intervention during delivery: n(%)	3 (30.0)	4 (57.1)	3 (75.0)

7.4.2 Maternal psychopathology in pregnancy and birth outcomes

Linear regression analyses were undertaken in order to investigate potential associations between maternal psychopathology during mid- and late pregnancy and primary obstetric outcomes (birth weight and length of gestation). Results of the analyses are shown in Table 7.4 and Table 7.5.

Mid-pregnancy

High EDE-Q scores in mid-pregnancy were associated with shorter length of gestation (coefficient = -0.3, 95% CI -0.62/-0.052, p=0.021), and to a lesser degree birth weight (coefficient= -87.9, 95% CI -182.9/7.1, p=0.069). After controlling for confounding variables (maternal age, ethnicity, parity and child gender) the relationship between EDE-Q scores and length of gestation persisted (adjusted coefficient= -0.36, 95% CI -0.66/-0.05, p=0.023), and the relationship between EDE-Q scores and birth weight reduced (adjusted coefficient= -65.7, 95% CI -169.1/37.7, p=0.21).

Including maternal smoking during pregnancy, gestational weight gain and other psychiatric history in the model further reduced the relationship between EDE-Q

scores and birth weight (adjusted coefficient = -60.2, 95% CI= -172.8/52.5, p=0.29), and EDE-Q scores and length of gestation (adjusted coefficient = -0.31, 95% CI = -0.68/0.056), p=0.095).

High BDI scores in mid-pregnancy were also associated with lower birth weights (coefficient= -19.4, 95% CI -35.3/-3.5, p=0.018), and a shorter length of gestation (coefficient= -0.05, 95% CI -0.10/-0.005, p=0.032). The relationship between BDI scores in mid-pregnancy and gestational length and birth weight reduced after controlling for confounding variables (maternal age, ethnicity, parity and child gender), see Table 7.4. Furthermore, after smoking during pregnancy and gestational weight gain were included in the model, some further attenuation of the relationship between BDI scores in mid-pregnancy and birth weight (adjusted coefficient = -12.9, 95% CI=-30.1/4.4), p=0.14) and length of gestation (adjusted coefficient = -0.048, 95% CI=-0.10/0.007, p=0.088) was apparent.

In mid-pregnancy, only modest associations were found between birth weight and: state anxiety (coefficient= -7.8, 95% CI -35.3/-3.5, p=0.13); trait anxiety (coefficient= -9.1, 95% CI -19.2/0.76, p=0.070); perceived stress (coefficient= -18.2, 95% CI -37.4/1.1, p=0.064) or pregnancy related anxiety (coefficient= -13.8, 95% CI -30.1/2.4, p=0.092). Which weakened after controlling for confounding variables, see Table 7.4. Similarly, gestational length was not associated with state anxiety (coefficient= -0.02, 95% CI -0.05/0.008, p=0.14); trait anxiety (coefficient= -0.01, 95% CI -0.04/0.02, p=0.32); perceived stress (coefficient= -0.04, 95% CI -0.09/0.002, p=0.20) and pregnancy related anxiety (coefficient= -0.04, 95% CI -0.09/0.008, p=0.10), in mid-pregnancy.

Table 7.4: Associations between maternal psychopathology in mid-pregnancy and obstetric outcomes

	Unadjusted			Adjusted [1]		
Birth Weight (g)						
	Coefficient	95% CI	p value	Coefficient	95% CI	p value
EDE-Q	-87.9	-182.9/7.1	0.069	-65.7	-169.1/37.7	0.21
BDI	-19.4	-35.3/-3.5	0.018	-13.0	-31.8/5.7	0.17
STAI state scores	-7.8	-18.1/2.4	0.13	-2.9	-14.6/8.7	0.61
STAI trait scores	-9.1	-19.2/0.76	0.070	-6.6	-18.2/4.9	0.26
PSS	-18.2	-37.4/1.1	0.064	-16.8	-40.7/7.0	0.16
PRA	-13.8	-30.1/2.4	0.092	-10.0	-27.5/7.4	0.25
Length of gestation (weeks)						
EDE-Q	-0.36	-0.62/-0.052	0.021	-0.36	-0.66/-0.05	0.023
BDI	-0.05	-0.10/-0.005	0.032	-0.058	-0.11/-0.002	0.043
STAI state scores	-0.02	-0.05/0.008	0.14	-0.023	-0.06/0.01	0.19
STAI trait scores	-0.01	-0.04/0.02	0.32	-0.019	-0.05/0.01	0.28
PSS	-0.04	-0.09/0.02	0.20	-0.047	-0.11/0.02	0.17
PRA	-0.04	-0.09/0.008	0.10	-0.042	-0.09/0.007	0.095

[1] adjusted for maternal age, ethnicity parity, and child gender

Late pregnancy

In late pregnancy, EDE-Q scores were no longer related to birth weight (coefficient= -75.6, 95% CI -175.3/24.0), p=0.13, which remained the case after adjusting for confounding variables, see Table 7.5. The relationship between EDE-Q scores and length of gestation in late pregnancy (coefficient= -0.30, 95% CI -0.61/0.007, p=0.056) was also weaker than in mid-pregnancy. After adjusting for confounding variables (maternal age, ethnicity, parity and child gender) this pattern remained similar, Table 7.5. Including smoking during pregnancy, gestational weight gain and other psychiatric diagnoses into the model, made little difference to the relationship between EDE-Q scores in late pregnancy and birth weight (adjusted coefficient = -56.8, 95% CI=-164.5/50.9, p=0.29) and length of gestation (adjusted coefficient = -0.33, 95% CI=-0.69/0.018, p=0.063).

High BDI scores in late pregnancy continued to be associated with lower birth weight (coefficient= -0.064, 95% CI -011/-0.018, p=0.007) and shorter length of gestation (coefficient= -21.5, 95% CI -36.2/-6.9, p=0.004), which persisted after controlling for confounding variables, Table 7.5. After including pregnancy smoking and gestational weight gain into the model the relationship between BDI scores and gestational length (adjusted coefficient = -0.08, 95% CI = -0.13/0.03, p=0.003) and birth weight (adjusted coefficient = -23.9, 95% CI = -39.3/8.5, p=0.003) persisted.

Similar to mid-pregnancy only modest relationships between birth weight and state anxiety (coefficient= -7.1 95% CI -17.9/3.6, p=0.18) and pregnancy related anxiety (coefficient= -13.3, 95% CI -0.29.2/2.7, p=0.10) were apparent in both unadjusted and adjusted analyses, Table 7.5. Higher levels of trait anxiety (coefficient= -12.1, 95% CI -23.5/-0.62, p=0.039) and perceived stress (coefficient= -20.5, 95% CI -29.2/2.7, p=0.037) were associated with lower birth weight deliveries. Some attenuation was observed after adjusting for confounding variables, see Table 7.5.

In late pregnancy, state anxiety (coefficient= -0.009, 95% CI -0.043/0.23, p=0.55); trait anxiety (coefficient= -0.015, 95% CI -0.52/0.022, p=0.42); perceived stress (coefficient= -0.041, 95% CI -0.036/0.0081, p=0.10) or pregnancy related anxiety (coefficient= -0.041, 95% CI -0.10/0.022, p=0.19) were not associated with length of gestation in both adjusted and unadjusted analyses, see Table 7.5.

Table 7.5: Associations between maternal psychopathology in late pregnancy and obstetric outcomes

	Unadjusted			Adjusted [1]		
			Birth Weight (g)			
	Coefficient	95% CI	p value	Coefficient	95% CI	p value
EDE-Q	-75.6	-175.3/24.0	0.13	-64.5	-180.1/51.0	0.26
BDI	-21.5	-36.2/-6.9	0.004	-27.9	-45.5/-10.4	0.002
STAI state scores	-7.1	-17.9/3.6	0.18	-7.2	-22.0/7.5	0.32
STAI trait scores	-12.1	-23.5/-0.62	0.039	-13.4	-28.4/1.5	0.078
PSS	-20.5	-39.7/-1.3	0.037	-23.8	-46.5/-1.2	0.040
PRA	-13.3	-29.2/2.7	0.10	-11.7	-28.6/5.2	0.169
			Length of gestation (weeks)			
EDE-Q	-0.30	-0.61/0.007	0.056	-0.43	-0.80/-0.069	0.021
BDI	-0.064	-0.11/-0.018	0.007	-0.11	-0.16/-0.059	<0.001
STAI state scores	-0.009	-0.043/0.023	0.55	-0.028	-0.074/0.018	0.23
STAI trait scores	-0.015	-0.052/0.022	0.42	-0.036	-.086/0.014	0.15
PSS	-0.041	-0.096/0.0081	0.10	-0.049	-0.11/0.005	0.074
PRA	-0.041	-0.10/0.022	0.19	-0.077	-0.15/0.0001	0.051

[1] adjusted for maternal age, ethnicity, parity and child gender

7.4.3 Maternal cortisol levels in pregnancy and birth outcomes

Multiple linear regression analyses, by maternal group, were undertaken to investigate the potential relationship between cortisol levels during pregnancy and main birth outcomes (i.e. birth weight and length of gestation). In unadjusted analyses, maternal cortisol levels on awakening or cortisol decline in mid-pregnancy were not associated with birth weight, in women with current or past ED or the healthy control group, see Table 7.6. After adjusting for confounding variables, maternal age, ethnicity, parity and child gender, higher cortisol declines were associated higher birth weights (adjusted coefficient=208.6, 95% CI=53.8/363.4, p=0.023) in women with active ED. Similarly, within the current ED group, high cortisol levels on awakening were associated with higher birth weight (adjusted coefficient=2408.8, 95% CI=1174.3/3643.3, p=0.008). After including maternal pre-pregnancy BMI and other psychiatric disorder history in the model, the relationship between cortisol decline and birth weight (coefficient=269.3, 95% CI=96.1/442.5, p=0.022) persisted in women with active ED. Some attenuation in the association between morning cortisol levels and birth weight was observed after including maternal pre-pregnancy BMI in the model and other psychiatric disorder history (coefficient=1208.1, 95% CI= -8659.2/3283.4, p=0.085).

By comparison, after adjusting for confounding variables, no associations between maternal cortisol levels in mid-pregnancy and birth weight were observed in the recovered ED or healthy control groups, see Table 7.6. Furthermore, in adjusted analyses no further associations between maternal cortisol and length of gestation were observed in women in the ED or non-ED groups, see Table 7.6.

In late pregnancy, there were no apparent associations between the decline in cortisol throughout the day or cortisol levels on awakening and birth weight or gestational length in any of the maternal groups. See Table 7.7. This pattern persisted after adjusting for potential confounding variables: maternal age, ethnicity, parity and child gender.

Table 7.6: Associations between log transformed maternal cortisol in mid-pregnancy and birth outcomes

	Mid-Pregnancy					
	Unadjusted[1]			Adjusted [2]		
	Birth weight					
	Current ED	Recovered ED	Healthy control	Current ED	Recovered ED	Healthy control
Cortisol Decline:						
coefficient	92.9	-5.1	24.4	**208.6**	-35.3	42.1
95% CI	-71.2/254.1	-80.2/69.9	-51.1/99.8	**53.8/363.4**	-132.3/61.7	-39.8/124.2
p value	0.22	0.88	0.21	**0.023**	0.43	0.29
Awakening:						
coefficient	1092.3	16.2	173.8	**2408.8**	-433.1	508.5
95% CI	-675.3/2859.9	-993.1/1025.54	-713/1061.6	**1174.3/3643.3**	-1866.8/1000.6	-460.0/1477.0
p value	0.18	0.97	0.68	**0.008**	0.51	0.28
	Length of gestation					
Cortisol Decline:						
coefficient	0.11	-0.068	-0.10	0.4	0.05	-0.06
95% CI	-0.52/0.75	-0.19/0.62	-0.07/0.27	-0.49/1.4	-0.26/0.17	-0.12/0.10
p value	0.68	0.27	0.25	0.22	0.62	0.51
Awakening:						
coefficient	1.2	-0.56	1.2	5.3	-0.39	0.89
95% CI	-5.8/8.3	-2.6/0.92	0.91/3.2	-5.1/15.8	-3.6/2.8	-1.3/3.1
p value	0.68	0.32	0.25	0.20	0.79	0.41

[1] controlling for time of wakening

[2] Adjusted for maternal age, ethnicity, parity and child gender

Table 7.7: Associations between log transformed maternal cortisol in late-pregnancy and birth outcomes

	Late-Pregnancy					
	Unadjusted[1]			Adjusted[2]		
	Birth weight					
	Current ED	Recovered ED	Healthy control	Current ED	Recovered ED	Healthy control
Cortisol Decline:						
coefficient	-40.7	-38.1	40.5	-35.7	-38.0	-43.5
95% CI	-117.3/35.8	-95.3/19.1	-25.8/106.8	-133.6/62.2	-122.6/46.6	-24.2/111.3
p value	0.27	0.16	0.22	0.44	0.31	0.19
Awakening:						
coefficient	376.4	-385.6	-392.6	-568.35	-374.4	379.9
95% CI	-646.5/1399.46	-1354.5/583.3	-875.2/90.0	-1645.8/509.1	-1651.5/-902.7	-767.5/1527.4
p value	0.45	0.41	0.10	0.27	0.50	0.49
	Length of gestation					
Cortisol Decline:						
coefficient	-0.0086	0.17	-0.05	-0.17	-0.05	-0.007
95% CI	-0.17/0.16	-0.54/0.21	-0.18/0.08	-0.5/0.21	-0.19/.079	-0.17/0.16
p value	0.92	0.34	0.38	0.69	0.37	0.92
Awakening:						
coefficient	-2.2	-0.36	-0.49	-2.9	-0.32	0.35
95% CI	-6.0/1.6	-1.3/0.6	-2.9/1.9	-6.8/1.0	-1.4/0.82	-2.9/2.2
p value	0.23	0.41	0.68	0.13	0.54	0.77

[1] controlling for time of wakening

[2] Adjusted for maternal age, ethnicity, parity and child gender

Table 7.8: Socio-demographic characteristics of mother-infant dyads at 8 weeks post-natal

	Current N=18	Recovered N=17	Healthy Control N=24
Maternal age: mean(s.d)	*28.3 (4.5)*	*31.8 (5.3)*	*32.7(4.9)*
Coefficient (95% CI), p value	*-4.6 (-3.7/-1.7) p=0.002*	*-0.8 (-3.7/213) p=0.56*	*Ref*
Pre-Pregnancy BMI: mean(s.d)	*22.7 (3.9)*	*24.2 (5.6)*	*22.5(3.1)*
Coefficient (95% CI), p value	*-0.8 (-3.1/1.6) p=0.52*	*1.6 (-0.7/4.0) p=0.17*	*Ref*
Married/Cohabiting: n(%)	13 (72.2)	13 (76.5)	22 (91.7)
OR (95% CI), p value	4.2 (0.71/25.0) p=0.11	3.4 (0.54/21.1) p=0.18	Ref
White ethnicity: n(%)	12 (66.7)	16 (94.1)	21 (87.5)
OR (95% CI), p value	1.6 (0.49/5.7) p=0.070	0.65 (0.06/1.3) p=0.15	Ref
Multiparity: n(%)	2 (11.1)	6 (35.3)	8 (33.3)
OR (95% CI), p value	0.3 (0.06/1.1) p=0.06	0.6 (0.2/2.8) p=0.45	Ref
Education: A-Levels/Higher: n(%)	16 (88.8)	13 (76.4)	21 (87.5)
OR (95% CI), p value	1.3 (0.16/10.4) p=0.92	1.6 (0.20/12.9) p=0.65	Ref
Pregnancy smoking: n(%)	3 (16.7)	1 (4.1)	0 (0)

7.4.4 Post-natal psychopathology and infant cortisol

Socio-demographic characteristics

Table 7.8 shows the demographic characteristics of women with available obstetric information across maternal group. The socio-demographic characteristics of the sub-sample of mothers completing post-natal assessments were comparable to the core sample of women completing pregnancy assessments.

Maternal psychopathology at eight weeks post-natal

EDE-Q scores in the subgroup of women who had completed assessments at 8 weeks post-natal remained different between the maternal groups ($F(1,49)=25.9$, $p<0.001$, $\eta^2=0.52$); and at 8 weeks post-natal EDE-Q scores remained higher in the current ED group (mean 2.4, s.d. 1.3), compared to the recovered ED group (mean 1.8, s.d. 1.2) and the healthy control group (mean 0.3, s.d 0.5). EDE-Q scores were found to significantly increase between late pregnancy and 8 weeks post-natal ($F(1,49)=6.1$, $p=0.017$, $\eta^2=0.11$). Post-hoc within group t-test revealed that EDE-Q scores remained relatively stable in the current ED and healthy control group, but increased from 1.1 (s.d. 1.1) to 1.8 (s.d. 1.2) ($p=0.004$) in the recovered ED group. See Table 7.10. In particular, shape and weight concerns were found to significantly increase in the recovered ED group in the post-natal period. However, no interaction effects between maternal group and change in EDE-Q scores were present ($F(2,49)=2.1$, $p=0.13$, $\eta^2=0.078$).

After controlling for covariates (maternal age, ethnicity and parity) only group differences remained $F(1,44)=24.1$, $p=<0.001$, $\eta^2=0.53$), and the main effect of assessment time on EDE-Q reduced ($F(1,44)=0.25$, $p=0.619$, $\eta^2=0.006$).

The number of women reporting objective and subjective binge eating remained relatively stable across the three groups between late pregnancy and 8 weeks post-natal, see Table 7.9. The number of women reporting an episode of SIV remained stable (2.5%) in late pregnancy and 8 weeks post-natal. However, the frequency of episodes of SIV continued to reduce in the post-natal period, from 6.2 (s.d. 2.8) to 3.6 (s.d. 3.2) episodes reported in the previous 28 days. Comparable to late pregnancy the number of women reporting an episode of laxative or diuretic use, or excessive exercise was relatively uncommon at eight weeks post-natal.

Table 7.9: Frequency n(%) of EDE-Q behaviours in late pregnancy and at eight weeks post-natal by maternal group

	late-pregnancy			***8 weeks post-natal***		
	Current n=17	Recovered n=17	Healthy Control n=24	Current n=17	Recovered n=17	Healthy Control n=24
Objective binge eating	7 (41.2)	4 (23.5)	3 (12.5)	8 (47.1)	4 (23.5)	4 (16.6)
Subjective binge eating	8 (47.1)	2 (22.2)	0	9 (52.9)	3 (17.6)	0
SIV	4 (23.5)	0	0	4 (23.5)	0	0
Laxative use	0	0	0	0	0	0
Diuretic use	0	0	0	1 (5.8)	0	0
Excessive exercise	0	0	0	2 (11.1)	2 (11.7)	0

BDI scores were found to decreased between late pregnancy and 8 weeks post-partum ($F(1,47)=5.2$, $p=0.028$, $\eta^2=0.09$). Group differences in BDI scores remained ($F(1,47)=102.9$, $p=0.004$, $\eta^2=0.21$) and BDI scores remained higher in the current and recovered ED group, compared to the healthy control group, but were comparable in the current and recovered ED groups, see Table 7.10. Post-hoc comparisons revealed that scores in the recovered ED group increased between late pregnancy and the post-natal period, but decreased in the current ED group; as such there was a significant interaction between ED group and BDI scores over time ($F(2,47)=3.6$, $p=0.034$, $\eta^2=0.13$). After controlling for covariates the main effect of assessment time on BDI scores were reduced ($F(1,44)=3.0$, $p=0.090$, $\eta^2=0.06$).

State anxiety decreased in the post-natal period ($F(1,49)=5.2$, $p=0.028$, $\eta2=0.099$), but remained higher in the current ED group (mean 37.2, s.d. 15.1) and the recovered (mean 36.7, s.d. 14.7), compared to the healthy control group (mean 29.6, s.d. 6.6),

see Table 7.10. Maternal group and assessment time interaction were present ($F(2,49)=3.6$, $p=0.034$, $\eta 2=0.13$). Post-hoc test indicated that state anxiety scores decreased in both the current and recovered ED groups, but increased in the healthy control group, see Table 7.10. Main effects of assessment time on state anxiety scores were no longer present after controlling for covariates ($F(1,46)=0.79$, $p=0.78$, $\eta 2=0.002$), interaction effects persisted with modest effect sizes ($F(2,46)=4.0$, $p=0.025$, $\eta 2=0.15$)

Group differences on trait anxiety remained in the post-partum ($F(1,50)=12.8$, $p<0.001$, $\eta^2=0.34$), and were higher in the current (mean 44.3, s.d. 12.1) recovered (44.2, s.d. 17.5) compared to the healthy control group (mean 31.6, s.d.6.9). Trait anxiety scores were stable between late pregnancy and 8 weeks post-natal in all groups ($F(1,50)=2.6$, $p=0.11$, $\eta^2=0.05$).

Table 7.10: Maternal psychopathology at late pregnancy and 8 weeks post-natal by maternal group

	Current n=17		Recovered n=17		Healthy Control n=24		Group Differences p value
	Late-pregnancy	***8 weeks post-natal***	***Late-pregnancy***	***8 weeks post-natal***	***Late-pregnancy***	***8 weeks post-natal***	
EDE-Q	2.4 (1.6)	2.4 (1.3)	1.1 (1.1)	1.8 (1.2)*	0.2 (0.2)	0.3 (0.5)	CED vs. HC: p<0.001 RED vs. HC: p=0.001 CED vs. RED: p<0.001
Restraint	1.5 (1.6)	1.8 (1.9)	0.6 (0.7)	1.1 (1.6)	0.2 (0.5)	0.2 (0.7)	
Weight concern	3.1 (1.8)	2.9 (1.6)	1.5 (1.5)	2.3 (1.4)*	0.2 (0.3)	0.4 (0.6)	
Shape concern	3.4 (1.7)	3.7 (1.8)	1.7 (1.5)	2.9 (1.5)*	0.2 (0.3)	0.6 (0.7)	
Eating concern	2.0 (1.6)	1.6 (1.3)	0.7 (0.9)	1.2 (1.1)	0.07 (0.2)	0.09 (0.1)	
BDI	15.3 (11.4)	9.5 (7.7)*	13.3 (9.0)	12.5 (10.3)	5.4 (2.8)	5.4 (4.3)	CED vs. HC: p<0.016 RED vs. HC: p=0.009 CED vs. RED: p=0.99
STAI-State	42.7 (11.7)	37.2 (15.1)	43.7 (15.2)	36.7 (14.7)*	27.9 (5.5)	29.6 (6.6)	CED vs. HC: p=0.007 RED vs. HC: p=.0004 CED vs. RED: p=0.647
STAI-Trait	49.8 (11.4)	44.3 (12.1)*	44.5 (11.9)	44.2 (17.5)	31.3 (3.5)	31.6 (6.9)	CED vs. HC: p<0.001 RED vs. HC: p=0.001 CED vs. RED: p=0.99
PSS	20.6 (6.5)	17.5 (7.2)	20.5 (6.6)	19.8 (9.8)	11.3 (3.7)	13.8 (6.1)	

**p<0.001 *p<0.01: within group differences based on paired t-test; CED=current ED group; RED=recovered ED group; HC= Healthy control group, between group differences based on post-hoc repeated measures ANOVA with bonferroni correction applied

7.4.5 Infant outcomes at eight weeks post-natal

There was a wide variation in infants' cortisol response to immunisations in all groups. Mean pre-immunisation cortisol levels were 7.0 nmol/L (s.d. 5.9) and mean post-immunisation cortisol levels were 8.8 nmol/L (s.d. 5.3), with a mean increase of 1.8 nmol/L (t(41)=1.8, p=0.078).

There was no difference in infant cortisol levels prior to the immunisations in either the current ED group (coefficient = -0.38, 95% CI = -4.8/4.05, p=0.86) or recovered ED group (coefficient=1.2, 95% CI=-3.1/5.4, p=0.57), compared to the healthy control group. Similarly, no difference in infants post-immunisation cortisol levels was observed in either the current ED group (coefficient = -0.56, 95% CI = -5.0/3.9, p=0.80) or recovered ED group (coefficient=0.54, 95% CI=-3.7/4.8, p=0.79), compared to the healthy control group. See Table 7.11.

As shown in Figure 7.1, infants of mothers with a current ED during pregnancy had a more pronounced cortisol response to the immunisations. Stress response in infants of women with current ED was 3.1 nmol/L (s.d. 5.8), 1.2 nmol/L (s.d. 6.7) in the recovered ED group and 1.6 nmol/L (s.d. 7.0) in the healthy control group. However, analysis indicated that the difference in cortisol response to the immunisations (controlling for the time of the immunisation) was not significantly different in the current (coefficient= 1.6, 95% CI= -3.7/6.9, p=0.54) or recovered ED groups (coefficient= -0.3, 95% CI= -5.2/-4.5, p=0.89), compared to the healthy control group. This remained the case after adjusting for confounding variables (child gender, birth weight, age, parity and maternal education), see Table 7.11.

On the day following the immunisations, infants' morning cortisol levels (controlling for time of waking) were significantly higher in current ED group (coefficient= 4.5, 95% CI= 0.2/8.9, p=0.043), but not the recovered ED group (coefficient= -0.9, 95% CI= -5.2.7/3.4, p=0.66) compared to the healthy control group. After adjusting for confounders (child gender, birth weight, age, parity and maternal education) infants' morning cortisol levels remained higher in the current ED group (adjusted coefficient= 6.5, 95% CI= 1.5/11.4, p=0.01). Post-hoc analyses revealed that after including state anxiety and depression scores during pregnancy in the model associations between current maternal ED and high morning cortisol persisted (adjusted coefficient = 13.2, 95% CI = 4.5/21.9, p=0.004). In contrast, inclusion of

post-natal anxiety and depression in the model reduced the association between active maternal ED during pregnancy and high infant cortisol levels (adjusted coefficient = 5.3, 95% CI = -2.1/12.8, p=0.150).

No differences in evening cortisol levels were found in the current ED group (coefficient= 2.1, 95% CI= -2.3/6.5, p=0.35) or the recovered ED group (coefficient= 3.2, 95% CI= -1.5/8.1, p=0.18), compared to the healthy control group. The remained the case in both the current ED group (coefficient= -0.08, 95% CI= -1.6/1.5, p=0.91) and recovered group (coefficient= 0.94, 95% CI= -2.4/0.53, p=0.20) after controlling for confounding variables.

Figure 7.1: Infant cortisol response to immunisations by maternal group

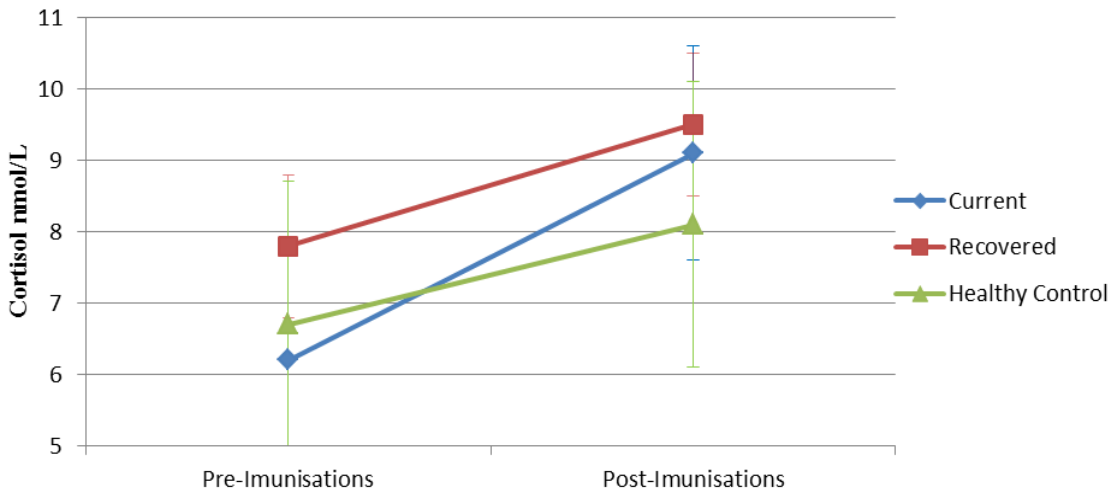


Table 7.11: Infant cortisol levels at 8 weeks post-natal by maternal group

	Unadjusted [1]			Adjusted [2]		
	Current n=12	Recovered n=14	Healthy Control n=19	Current n=12	Recovered n=14	Healthy Control n=19
Pre-immunisations: mean (s.d.)	6.2 (4.5)	7.8 (6.2)	6.6 (6.5)			*Ref*
Coefficient	-0.38	1.2		-2.1	1.8	
(95% CI)	-4.8/4.05	-3.1/5.4	Ref	-6.9/2.7	-3.0/6.7	
p value	p=0.86	p=0.57		p=0.37	p=0.45	
Post-immunisations: mean (s.d.)	9.1 (4.8)	9.5 (6.4)	8.1 (5.8)			*Ref*
Coefficient	-0.56	0.54		-0.3	2.2	
(95% CI)	-5.02/3.9	-3.7/4.8	Ref	-5.6/4.9	-3.1/7.5	
p value	p=0.80	p=0.79		p=0.89	p=0.41	
Stress response: mean (s.d.)	3.1 (5.8)	1.2 (6.7)	1.6 (7.0)			*Ref*
Coefficient, (95% CI)	1.6	-0.3		1.6	-2.2	
p value	(-3.7/6.9)	(-5.2/-4.5)	Ref	(-9.7/6.6)	(-9.8/-5.4)	
	p=0.54	p=0.89		p=0.69	p=0.59	
Day 2: Morning: mean (s.d.)	10.3 (9.3)	4.8 (3.1)	5.7 (4.1)			*Ref*
Coefficient	4.5	-0.9		6.5	-1.2	
(95% CI)	0.2/8.9	-5.2.7/3.4	Ref	1.5/11.4	-6.0/3.7	
p value	p=0.043	p=0.66		p=0.01	p=0.64	
Day 2: Evening mean (s.d.)	6.1 (5.7)	7.4 (9.2)	4.1 (4.2)			*Ref*
Coefficient	0.008	-0.42		0.08	-0.94	
(95% CI)	-1.3/1.3	-1.5/0.68	Ref	-1.6/1.5	-2.4/0.53	
p value	p=0.99	p=0.44		p=0.91	p=0.20	

[1] controlling for time of immunisation/time of wakening

[2] adjusted for child gender, age, birth weight, parity, maternal education

7.5 Discussion

This study aimed to investigate obstetric outcomes and potential associations with maternal psychopathology and cortisol levels during pregnancy in women with past and active ED, compared to women without ED. Furthermore, infant cortisol levels and maternal psychopathology in the post-natal period were examined.

7.5.1 Obstetric outcomes

In this investigation, contrary to the hypothesis, birth weight and length of gestation were found to be comparable in women with active or past ED in pregnancy, compared to women without ED. Despite the lack of differences on continuous variables of birth weight and length of gestation, 19% of women with current ED were found to deliver prematurely. Furthermore, ED symptoms during pregnancy were found to be associated with a shorter gestational length, and to a lesser degree lower birth weight.

Two recent investigations of birth outcomes in women with ED from large prospective birth cohorts have reported conflicting findings (Bulik, et al., 2009; Micali, Simonoff, et al., 2007a). Bulik and colleagues (Bulik, et al., 2009) found that the length of gestation and birth weights in women with AN and BN during pregnancy were comparable to women without ED. In contrast to previous studies in clinical samples (Ekeus, et al., 2006; Koubaa, et al., 2005; Sollid, et al., 2004; Waugh & Bulik, 1999), the author reported that the risk of preterm delivery was found to be reduced in women with AN (Bulik, et al., 2009). It was further postulated that, adequate gestational weight gain in this sample may have been protective against adverse birth outcomes in women with ED. In comparison, the relationship between birth weight and gestational length and ED symptoms during pregnancy in the present investigation was only modestly affected after controlling for maternal characteristics such as age, pregnancy smoking and gestational weight gain.

In contrast to the findings of Bulik and colleagues described above, birth weights of offspring born to women with a recent episode of AN in ALSPAC were found to be reduced, while gestational length was comparable to women without ED. In this study Micali et al (2007a) reported that the average birth weight of women with a recent episode of AN was 3,340g, which is higher than the birth weight of women with current AN (3,136g) in the present investigation. Therefore, it is possible that the small sample

size in the present investigation reduced the power to detect these differences. Furthermore, there was some indication that birth weights were lower in women with AN compared to women with BED. It has previously been reported that women with BED have an elevated risk of delivering babies that are large for gestational age (Bulik, et al., 2009). Therefore, grouping women with AN and BED during pregnancy in the present investigation may have reduced potential effects of ED sub-type on birth weight.

7.5.2 Mechanisms of risk

The potential mechanisms underlying birth outcomes in women with ED have been highlighted by Micali and Treasure (2009) in a biological model of risk (see Figure 1.2, in section 1.7 'Hypothetical models of risk'). Two pathways are hypothesised in this model: poor nutrition (e.g. protein restriction) and co-morbid anxiety and depression in women with ED during pregnancy. These pathways are thought to be mediated by increased levels maternal CRH, and in turn, elevated levels of glucocorticoids (cortisol) in the foetal circulation.

Maternal psychopathology during pregnancy

Despite the lack of differences in birth outcomes in the present investigation, several associations between maternal psychopathology and birth outcomes were observed. ED symptoms during pregnancy were associated with a shorter length of gestation, which was not accounted for by socio-demographic factors, co-morbid psychopathology or gestational weight gain. Nevertheless, depressive symptoms during pregnancy independently increased the risk of lower birth weights and shorter gestations. Furthermore, in the present study, symptoms of stress and anxiety, specifically perceived stress and trait anxiety, were associated with reduced birth weights. This is in line with previous investigations, which have highlighted that psychological stress or anxiety during pregnancy increases the risk of adverse birth outcomes, such as premature deliveries (Glynn, et al., 2008; Hedegaard, et al., 1993), and provide support for the biological model of risk proposed by Micali and Treasure (2009). However, the relationship between state and trait anxiety and birth outcomes was modest, particularly in mid pregnancy. Since a history of psychiatric illness was an exclusion criterion from the healthy control group, low levels of anxiety in this group may have weakened the relationship between state anxiety and birth outcomes in this particular study.

Maternal cortisol during pregnancy

There is strong evidence from animal studies that one of the meditational pathways of psychosocial stress in pregnancy and birth outcomes is via elevated stress hormones, such as cortisol and CRH (Wadhwa, et al., 2004). Recently, support for this in studies with humans is emerging (Berkowitz, et al., 2003; Buss, et al., 2009; Hobel, Dunkel-Schetter, Roesch, Castro, & Arora, 1999; Mazor, et al., 1994). However, in contrast to previous reports (Kivlighan, et al., 2008), high morning cortisol levels and a higher cortisol decline across the day in the present investigation, during mid-pregnancy, were found to be associated with higher birth weights in women with active ED.

It was hypothesised in the previous chapter (Chapter 6, section 6.5) that low morning cortisol levels observed in women with ED may be protective against adverse obstetric outcomes, such as prematurity and low birth weight. However, findings from the present investigation do not support this hypothesis. Nevertheless, flatter declines in cortisol throughout the day were also observed in women with ED during mid-pregnancy, and associated with reduced birth weights in women with active ED. As previously discussed, flatter cortisol declines are thought to reflect less recovery from high morning cortisol levels and thus higher evening cortisol. Therefore, within group diurnal patterns of cortisol may be a risk factor for lower birth weights in women with ED, and the pattern of daily declines in cortisol may be an important indicator of HPA axis functioning in women with ED during pregnancy and requires further investigation.

Few studies have investigated diurnal patterns of cortisol during pregnancy in relation to maternal psychopathology and birth outcomes. Although it has been demonstrated that sufficient levels of cortisol can cross the placenta (Gitau, Fisk, & Glover, 2004), and some studies have found associations between maternal stress hormones during pregnancy and birth outcomes (Diego, et al., 2006; Wadhwa, et al., 2004), the magnitude of effects has varied across studies. Nevertheless, the physiology of the stress system is complicated and the associations with birth outcomes are not yet fully understood (Wadhwa, Entringer, Buss, & Lu, 2011). Furthermore, it is unlikely that a single measure of HPA axis functioning during pregnancy, such as cortisol, would be able to fully explain the relationship between stress and birth outcomes and neuroendocrine, vascular and immune processes during pregnancy are all likely to be involved (Wadhwa, et al., 2011). Further investigation of HPA axis activity during

pregnancy, such as alterations to CRH levels and 11 β-HDS2 activity, in this group of women may help elucidate the relationship between cortisol levels in pregnancy in women with active ED and birth outcomes.

In order to inform future investigations in this area it is important to consider alternative mechanisms and pathways of obstetric complications in women with ED. For example, it has been proposed that stress may exert effects on the foetus via reduction of intrauterine blood flow, and therefore vascular transportation of oxygen and nutrients to the foetus. Furthermore, Micali and Treasure (2009) propose that nutritional intake during pregnancy in women with ED is also likely to exert both indirect (via alterations in maternal HPA axis functioning) and direct effects (via low folate and hypoglycaemia) on foetal development. Investigations of the effects of nutrition during pregnancy in women with ED, and interactions with stress systems, on birth outcomes, will be an important area of future investigation.

Critical periods

It is possible that there are critical periods where the foetus may be more vulnerable to exposure to elevated stress (Wadhwa, et al., 2011). In the present investigation, high levels of psychosocial stress and anxiety in late pregnancy were more strongly associated with lower birth weights than in mid-gestation. By comparison, maternal cortisol levels during mid-pregnancy were more strongly associated with birth weight in women with ED. Hedegarrd and colleagues (1993) reported that that general stress and anxiety in late pregnancy, but not at 16 gestation, weeks was predictive of shorter lengths of gestation.

It has recently been postulated that patterns of stress/anxiety and cortisol levels during pregnancy may also be important. For example, Glynn (2008) and colleagues highlighted that increases in stress and anxiety across pregnancy, rather that levels of stress at a given gestation, were associated with preterm deliveries. Furthermore, recent reports suggest that the trajectory of diurnal cortisol rhythms across gestation may also be a more important indicator of birth outcomes (Buss, et al., 2009). Therefore, future investigations should additionally examine patterns of maternal stress across gestation and potential associations with birth outcomes.

7.5.3 Post-natal maternal psychopathology

In the present investigation, women with active ED continued to experience high levels of ED symptoms in late pregnancy, which remained relatively stable in the post-natal period. In contrast, ED symptoms, in particular shape and weight concerns, were found to increase in the post-natal period in women with a past history of ED. This finding is in line with previous reports that the post-natal period is a high risk time for recurrence of ED symptoms in women with a history of ED (Micali, Treasure, et al., 2007b; Morgan, et al., 1999c). Previous reports have tended to investigate ED symptoms later in the post-natal period than in the present investigation (Lemberg & Phillips, 1989; Morgan, et al., 1999c). Findings from the present investigation highlight that the risk of resurgence in ED symptoms for women with a history of ED may occur very early on in the post-natal period, and further demonstrate the need for additional support and continuity of care in the post-natal period for women ED. Furthermore, it will be important to determine whether this observed increase in ED symptoms in women with past ED is temporary or reflects a more long-standing relapse of symptoms following pregnancy.

In contrast to other studies (Franko & Spurrell, 2000; Morgan, et al., 1999c; Morgan et al., 2006), depression was shown to further reduce in women with ED in the post-natal period. This discrepancy may also be due to the differing length of post-natal follow-up assessment; alternatively the use of a more general measure of depression rather than specific post-natal depression may have underestimated levels of post-natal depression in this study. It will be important to continue to investigate the trajectory of psychopathology in this group of women during the post-natal period.

Women with current and past ED also experienced a reduction of anxiety in the post-natal period. In previous investigations presented in this thesis, pregnancy related anxiety was found to be significantly elevated in women with both past and current ED (see Chapter 6) and women with ED more frequently experienced negative feelings regarding their pregnancy (Chapter 3). Given the reductions in anxiety found in this study, it is likely that the pregnancy itself contributed to high levels of anxiety during pregnancy in this group of women. Therefore, interventions during pregnancy for women with ED should be target at reducing specific pregnancy related anxieties as well as more general anxiety.

7.5.4 Infant cortisol

As hypothesised, infant cortisol response to a painful stressor (immunisations) was found to be twice as high in infants of women with active ED during pregnancy, compared to infants of mothers with no ED. However, this finding was not statistically significant and it is possible that due to the small sample size, and wide variations in infants stress reactivity, the present investigation may have lacked the power to detect differences. Additionally, morning cortisol levels in infants of women with active ED were elevated compared to infants of women without ED. No previous studies have investigated cortisol levels in infants of women with ED, therefore, further investigation and replication is required in larger samples. Nevertheless, these findings are in line with previous investigations which suggest that maternal anxiety or depression during pregnancy is associated with elevated cortisol levels in their infants (Davis, et al., 2011; Field, et al., 2004; Gutteling, et al., 2004; Gutteling, et al., 2005; O'Connor, et al., 2002).

The finding of elevated cortisol levels in infants of women with ED is important since previous research has indicated that altered functioning of the HPA axis in infancy is linked to deficits in cognitive performance (Gué, et al., 2004) heightened emotionality (Weinstock, 1997) and behavioural problems (Griffin, et al., 2003). Furthermore, infant stress regulation may be an early risk factor for developmental problems and psychopathology. Recently, stress regulation, and interactions with obstetric complications, has also been implicated as a risk factor for the development of AN (Favaro, Tenconi, et al., 2008; Favaro, et al., 2010). Therefore, it will be important to continue to follow-up these infants and mothers during childhood.

It is difficult to separate pre- and post-natal effects in investigations of infant cortisol levels, as well as the environmental and genetic contributions. Mothers who are stressed or anxious during pregnancy are also likely to be stressed in the post-natal period. Furthermore, environmental influences, such as social support and paternal factors are all likely to contribute. Further investigation is therefore required to examine the potential mechanisms for elevated cortisol in infants of women with active ED. Preliminary analyses in the present investigation suggested elevated cortisol levels in infants of women with active ED were not accounted for by maternal socio-demographic factors, birth weight, or pre-natal anxiety and depression. By comparison,

the relationship between maternal ED and elevations in infant stress response appeared in part to be mediated by maternal post-natal anxiety and depression.

7.5.5 Strengths and limitation

The main strength of this study is its uniqueness to investigate the contribution of psychological and biological markers of maternal psychopathology during pregnancy to obstetric outcomes in women with ED. Furthermore, this is the first investigation to measure cortisol levels in infants of women with ED. The women and infants were followed up prospectively, and extensive validated measures of psychopathology and stress were employed. Furthermore, ED classification and other psychiatric diagnoses were made on the basis of diagnostic interview.

The main limitation of this investigation is that the overall sample size and number of women in each group was small, and some further attrition occurred in investigations of birth outcomes. Investigations of post-natal maternal psychopathology and infant cortisol levels were only carried out in a sub-sample of the core sample of participants completing pregnancy assessments, which further reduced the sample size. Therefore, it will be crucial to continue to investigate the remaining sample of mother infant-dyads in order to validate the findings of the present investigation. Although several confounding variables were accounted for in the present investigation, the associations examined in the present investigation are likely to be influenced by a wide variety of factors. In particular, paternal factors were not investigated in this study.

This investigation is also subject to some of the limitations presented in the previous chapter (see section 6.5.3). For example, due to small sample size it was not possible to assess potential differences between different ED sub-types; furthermore only a single measure of HPA axis functioning was employed, salivary cortisol, and more extensive measures would strengthen the present investigation.

7.5.6 Conclusions and clinical implications

In conclusion, although few differences were apparent in terms of birth outcomes in women with ED, increased symptoms of ED, stress and anxiety during pregnancy were associated with reductions in birth weight and length of gestation. Furthermore, patterns of diurnal cortisol during of women with active ED in mid-pregnancy were independently associated with birth weight. Associations between maternal ED

symptoms in pregnancy and diurnal cortisol rhythm suggest a potential mediating role specific to ED psychopathology during pregnancy. This is the first investigation to examine the relationship between maternal psychopathology and cortisol levels during pregnancy in women with ED and further replication of these findings is required.

In general, in the early post-natal period symptoms of ED, depression and anxiety were relatively stable in women with active ED, or further reductions in symptoms were apparent. On the other hand, women with a history of ED were found to experience an increase in ED symptoms in the post-natal period, further highlighting the need to monitor psychopathology both during pregnancy and in the post-natal period of women with a history of ED.

Additionally, it was demonstrated in the present investigation that infants of women with ED had an increased risk of elevated cortisol levels. Since dysfunctions in HPA axis activity during childhood may represent a risk factor for psychological and health problems later in life, replication of this finding and further investigation of the potential long-term implications will be crucial.

Chapter 8. General Conclusions and Clinical Implications

8.1 Chapter overview

This chapter provides a summary of the main findings from the investigations undertaken within this thesis, with reference to prior literature and the aims and objectives previously outlined. Following which the key strengths and limitations will be summarised, and suggestions will be made for future research. Finally, the clinical implications of this research will be considered.

8.2 Summary of findings

The overall aim of this thesis was to investigate the effects of maternal ED on fertility and pregnancy, as well the associations with birth outcomes and infant cortisol levels. In addition, investigations were aimed at examining the dietary patterns and growth trajectories of children of women with ED, compared to children of women without ED. Five studies, based on previous literature, were undertaken to focus on these specific aspects of ED and motherhood and outcomes in their offspring.

8.2.1 Eating disorders in the pre-conception period

Study one aimed to expand the knowledge base on the relationship between ED and fertility, specifically the aim was to investigate whether ED affect the length of time taken to conceive, and the amount of help or advice sought for fertility problems. The findings suggest that women with ED experience more difficulties conceiving. Specifically, it was found that women with lifetime AN were nearly twice as likely to have seen a doctor for a fertility problem, and more frequently reported receiving help or treatment to conceive. Previous research in this area has been limited since it focuses on samples drawn from clinical services such as infertility clinics and specialist ED services, and the length of time taken to conceive may be a more sensitive measure of fertility problems. Within this investigation, although few women took longer than one year to conceive, women with a history of both AN and BN were more likely to take longer to conceive than women without ED. This is in line with previous findings which have suggested that a high proportion of women attending fertility clinics have an ED (Freizinger, et al., 2008; Stewart, et al., 1990).

8.2.2 Eating disorders and pregnancy

Specific aims of this thesis were to investigate the prevalence of unintentional pregnancies and pre-natal feelings towards pregnancy in women with ED, compared to women without ED. Potential changes in maternal ED symptoms and co-morbid symptoms of depression and anxiety during pregnancy were also investigated. Furthermore, diurnal salivary cortisol rhythms during pregnancy and associations with maternal psychopathology during pregnancy in women with ED were examined.

Unintentional pregnancies and pre-natal bonding

As hypothesised, unintentional pregnancies were common in women with ED. Specifically, over 40% of women with a history of AN reported that their pregnancy was unplanned. By comparison, the frequency of unintentional pregnancies was more comparable in women with BN to women without an ED. This finding confirms recent findings from a large Norwegian birth cohort (MoBa), which found that over half of the women with AN reported that their pregnancy was unplanned (Bulik, et al., 2009).

In addition, women with ED, particularly women with a history of both AN and BN, more frequently experienced negative feelings about their pregnancy at 12 weeks gestation; although these negative feelings had typically reduced by 18 weeks gestation they continued to remain more common in women with ED. Few studies have examined how women with ED feel about their pregnancy in the pre-natal period, nevertheless this finding is in line with previous reports that women with ED experience difficulties adjusting to motherhood (Koubaa, et al., 2008). Mothers with ED have been identified as an at risk group for experiencing problems with attachment in the post-natal period (Astrachan-Fletcher, et al., 2008) and pre-natal feelings towards pregnancy may be an early risk factor for post-natal attachment difficulties.

Maternal psychopathology during pregnancy

In a separate investigation of this thesis, as hypothesised, women with active ED had a reduction in ED symptoms during pregnancy. Nevertheless, ED symptoms remained high, and over 20% of women continued to engage in SIV in late gestation. These findings are in line with evidence from previous studies, which suggested that ED symptoms reduce during pregnancy (Bulik, et al., 2007; Micali, Treasure, et al., 2007b);

nevertheless it is important to acknowledge that this does not represent a complete remission of ED during pregnancy.

Symptoms of anxiety were also found to be persistently high during pregnancy for women with past and active ED, and only minimal reductions were apparent during pregnancy. Few studies have investigated co-morbid psychopathology during pregnancy in women with ED. The findings from this study are in line with a previous investigation of women in the ALSPAC (Micali, et al., in press), which suggested that high levels of anxiety and depression were common in women with ED during pregnancy and the post-partum. Given the potential associations between pre-natal anxiety and birth complications (Wadhwa, et al., 2011), the persistently elevated levels of anxiety during pregnancy in women with ED has important implications for the treatment of women with ED during pregnancy.

Diurnal cortisol rhythms during pregnancy

It was demonstrated that women with active ED display differential diurnal cortisol levels during pregnancy, which are characterised by low morning cortisol levels and a flatter decline in cortisol throughout the day. In this investigation, low morning cortisol levels were associated with higher levels of ED symptoms in mid-pregnancy; on the other hand, cortisol levels were only modestly related to symptoms of depression, anxiety and stress during pregnancy. It has previously been postulated that elevated cortisol levels during pregnancy may contribute to adverse perinatal outcomes in women with ED (Micali & Treasure, 2009). Although women with active ED were found to have low morning cortisol, compared to women with a prior history of ED and those without ED, they demonstrated a lower decline in cortisol throughout the day.

Lower declines in cortisol throughout the day, which may be a more subtle marker of HPA axis functioning in pregnancy, have previously been associated with elevated pre-natal stress during pregnancy (Obel, et al., 2005), which may have implications for levels of stress hormones in foetal circulation. No previous studies have investigated cortisol levels in women with ED during pregnancy, and this is the first study to highlight the relationship between active ED symptoms and patterns of cortisol production during pregnancy. Further replication of this finding in larger samples will be crucial.

8.2.3 Obstetric outcomes in women with eating disorders

The overall aim of the final study of this thesis was to examine obstetric complications and *in utero* risk factors (maternal psychopathology and cortisol levels) for birth outcomes in infants of women with active and remitted ED, compared to women without ED. Despite comparable birth weights and lengths of gestation in women with and without ED, 19% of women with active ED during pregnancy delivered prematurely and birth weight was particularly low for women with AN. Furthermore, the findings from this investigation indicate that maternal psychopathology and cortisol rhythms might be associated with birth outcomes in women with active ED. Specifically, high levels of psychopathology during pregnancy were found to be associated with lower birth weights and shorter gestations. In addition, low morning cortisol and flatter declines in cortisol across the day, during mid-pregnancy, were associated with lower birth weights in women with active ED.

This is the first investigation to examine potential *in utero* risk factors for birth outcomes in women with ED during pregnancy. In support of the biological model of risk proposed by Micali and Treasure (2009), ED symptoms and, co-morbid anxiety and depression during pregnancy were associated with lower birth weights and a shorter length of gestation. Furthermore, diurnal cortisol patterns during pregnancy independency predicted lower birth weights in women with ED. Replication of these findings is required, as is further exploration of additional potential mechanisms for obstetric outcomes in women with ED.

8.2.4 The post-natal period

The final study of this thesis also aimed to investigate changes in maternal psychopathology (ED, anxiety and depression), as well as infant cortisol levels and stress response, at 8 weeks post-natal in women with and without ED during pregnancy.

Maternal psychopathology

In the early post-natal period, maternal ED symptoms, anxiety and depression remained relatively stable or further reductions were observed in women who had active episode of ED during pregnancy. This finding is in contrast to several studies, which have highlighted that the post-natal period is a time of increased risk for women with ED, specifically for a relapse of ED symptoms and post-natal depression (Morgan, et al,

2006; Micali, et al., 2010). In comparison to previous studies, the post-natal period investigated within this thesis was earlier, furthermore fewer reductions in psychopathology were observed during pregnancy than in previous investigations, this highlights the need for continuity of care in the post-natal period in order to maintain potential improvements in symptoms achieved during pregnancy and to reduce the risk of relapse.

By comparison, ED symptoms in the post-natal period, particularly weight and shape concerns, increased in women who had recovered from an ED prior to pregnancy, it will be important to determine whether this is just a temporary increase in symptoms or represents a relapse in the post-natal period.

Infant cortisol levels

The findings from this pilot investigation indicate that infants of women with active ED during pregnancy may have an increased risk for elevated cortisol levels. Specifically, in line with the hypothesis of this investigation, morning cortisol levels were found to be elevated in infants of women with active ED during pregnancy. Furthermore, infants of women with active ED displayed a cortisol response to a stressful situation that was twice as high as infants of women without an ED. Although pre-natal anxiety had little effect on infant cortisol levels in this study there was some indication that post-natal maternal anxiety and depression may play a meditational role in elevated infant cortisol levels.

No previous investigations have examined cortisol levels in the offspring of women with ED, and the findings from this study may have important implications for their development during childhood. Previous studies have indicated that elevated cortisol levels in infancy, as a marker of HPA axis dysfunction, are an early risk factor for behavioural and developmental problems during childhood (O'Connor, et al., 2002), and future depressive disorders and psychological disturbances (Essex, Klein, Cho, & Kalin, 2002). Furthermore, it has been theorised that HPA axis dysfunction may be implicated in the pathogenesis of ED (Favaro, et al., 2010). The findings from the present investigation are derived from a pilot investigation and replication in larger samples, as well as examination of long-term implications is important.

8.2.5 Diet and growth in children of women with eating disorders

The aims of study two and three were to explore potential differences in adherence to dietary patterns and macronutrient intake between the ages of three and nine, and growth trajectories between birth and ten in children of women with ED, compared to children of women without ED.

Dietary patterns and macronutrient consumption

Contrary to the hypotheses of this investigation, the findings indicate that adherence to 'processed' and 'junk' dietary patterns is similar in children of mothers with and without ED. Despite this finding, children of women with a lifetime history of BN consumed more sugar, fat, starch, protein during childhood than children of women without a history of ED. Furthermore, children of women with ED adhered less to a 'traditional dietary pattern', which consisted of foods that would typically be eaten during mealtimes. This finding may be reflective of previous reports that have suggested that family mealtimes can be challenging for women with ED and evoke greater levels of conflict (Stein, et al., 1999).

This study also indicates that children of women with ED, particularly female children of women with AN, are more likely to adhere to a 'health conscious' dietary pattern during childhood. This finding persisted after accounting for maternal factors known to affect childhood dietary patterns. It has previously been demonstrated that women with ED were more likely to adhere to this dietary pattern in pregnancy (Micali, et al., in press), and therefore may reflect a stronger desire in women with ED to provide a health conscious diet for their children.

In later childhood, children of women with ED showed reduced adherence to the 'health conscious' dietary pattern and greater adherence to the 'traditional' dietary pattern, which may reflect other societal influences such as school or the children taking more control over their diet. However, the long-term implications of greater adherence to this dietary pattern for children of women with ED are currently not known, and provide an important area for future research.

Growth trajectories

No previous investigations have examined growth trajectories longitudinally in children of women with ED and it is reassuring that there no gross deficits in the growth of

children of mothers with ED were observed in this study. However, some noteworthy gender specific differences in growth were apparent. The findings from this study indicate that children of women with a history of BN have a tendency to be taller throughout childhood, and have higher BMI at certain stages. Specifically, male children of women with a history of BN were found to be taller throughout childhood, and had a higher BMI between the ages of one and five years, compared to children of women without an ED history. Furthermore, female children of women with BN were also found to have a higher ponderal index at birth and BMI at five years of age, compared to children of women with no ED. In line with the hypotheses of this investigation, this finding to some extent supports previous reports from clinical samples, which suggested that children of women with BN have a risk of being overweight or obese (Hodes, et al., 1997; Micali, et al., 2009; Stein & Fairburn, 1989), and may have important health implications. Furthermore, increased growth in male children of women with ED appeared to be specific to maternal ED since male children of women with other psychiatric tended to be shorter and have a more comparable BMI trajectory to children of women without a history of psychiatric illness.

Fewer differences were apparent in female children, although female children of women with ED tended to be shorter throughout childhood, compared to female children of women without ED. This was particularly the case for children of women with AN in early infancy, and was not influenced by maternal socio-demographic factors or maternal BMI. However, the reduced height observed in females was not specific to children of women with ED since reduced height was also observed in female children of women with other psychiatric disorders.

8.3 Strengths and limitations

Specific strengths and limitations have been highlighted and discussed in detail throughout this thesis, a general overview of the main issues pertaining to the investigations included in this thesis are highlighted below.

8.3.1 General strengths

The main advantage of investigations utilising data from ALSPAC (Chapters 3, 4 and 5) is that it is a large prospective cohort, which is representative of the study area and comparable to Great Britain as a whole. This allowed for the hypotheses generated from

previous clinical samples to be explored in a larger community sample, and overcomes many of the limitations of several previous investigations. Furthermore, extensive information was available on confounding variables, which enabled a less bias investigation to be undertaken. Repeated measurements of the diet and growth of the children involved in ALSPAC throughout childhood also allowed for a longitudinal investigation of childhood diet and growth. Examination of trajectories and patterns, rather than data from a single time-point has not been reported on previously in the children of women with ED.

Recruitment of a separate cohort of participants further strengthens the investigations undertaken in this thesis, since it allowed for the examination of unique aims and hypotheses, where data were not available within ALSPAC. Furthermore, it was possible to ascertain full psychiatric diagnoses and the course of ED symptoms across pregnancy; this facilitated the ability to investigate the relationship between active and remitted ED symptoms during pregnancy and birth and infant outcomes.

8.3.2 Participants and sample size

Specific issues relating to participants and sample size have been discussed throughout this thesis. The ALSPAC is a birth cohort, and by definition the women involved in the study were able to become pregnant; therefore, they are likely to represent a cohort of women with less severe ED than those presented in previous studies of clinical samples, which may account for some of the differences in findings. If this is the case it is possible that the conclusions presented in this thesis are an underestimation rather than an overestimation of the findings. Despite the large sample size of ALSPAC the number of women with ED in each group was relatively small, and therefore certain studies may have lacked power to detect differences, and increased the risk of type II errors.

On the other hand, the participants involved in studies presented in the second half of this thesis (Chapters 6 and 7) were mainly identified via specialist services and therefore may not be representative of women with ED in the general population. Furthermore, the sample size of participants was small and replication of the findings presented in these studies will be important.

8.3.3 Eating disorder classification

An additional strength of the studies utilising data from ALSPAC allowed for comparisons between ED sub-types. Nevertheless, since the data was based upon self-reported ED status it may not directly related to ED diagnosis if made by a trained clinician. Therefore, the main limitation of the ALSPAC study included is that ED classification was based upon self-report, which may be subject to bias and not accurately reflect DSM ED diagnosis. Furthermore, it was only possible to classify women according to lifetime ED, and therefore active ED symptoms and behaviours could not be mapped onto the outcomes investigated. By comparison, in the NEST-p sample although detailed information was available on the course of maternal psychopathology during pregnancy, due to small sample size it was not possible to compare outcomes between ED sub-types in these investigations. Some differences between women with AN, BN and BED were apparent, and grouping participants into one comparison group may have weakened potential effects.

8.3.4 Paternal factors

The focus on the present thesis was to further understand the effect of maternal ED on pregnancy and motherhood, therefore similar to previous studies in this field, the role of the father and paternal factors were not investigated. Very little has been written about fathers in the context of families where a mother has an ED, and it is unclear whether fathers have a protective, exacerbating or an independent effect on birth and child outcomes (Patel, et al., 2002). In order to gain a fuller understanding of mother-child effects in families where a mother has an ED it will be important to consider the full family context as an integrative unit and impact of parental factors.

8.4 Future research

Several potential areas for future research have been generated from the investigations undertaken in this thesis, and are highlighted throughout. Several specific suggestions are outlined below.

This is the second large epidemiological study to demonstrate that the risk of unplanned pregnancies is significantly elevated in women with AN. In order to provide appropriate pre-conception advice and support, future research investigating the potential contributions to unplanned pregnancies in women with AN will be important.

Furthermore, examining the implications of increased negative feelings towards pregnancy in women with ED, indicative of poor pre-natal bonding, on post-natal attachment and bonding will be an important area of future investigation.

The investigations presented in this thesis highlight some important gender specific differences in the dietary patterns and growth trajectories of children of women with ED. This is the first investigation of diet and growth at multiple time-points during childhood in the offspring of mothers with ED, and replication of these findings in other large samples is important. Furthermore, a follow-up assessment of these children during adolescence is crucial in order to examine the long-term implications of differences in childhood dietary patterns and growth trajectories. This will be relevant both to determine any potential long-term implications on their health and development, and also for their development of attitudes and behaviours towards diet, weight and shape. Future research should also focus on the potential mechanisms for diet and growth in the children of women with ED, as well as the relationship between the two.

Pilot investigations undertaken in this thesis highlight some important differences in diurnal cortisol rhythms in women with active ED during pregnancy. Replication of these findings is important, as are further investigation of the underlying mechanisms of cortisol patterns during pregnancy in women with ED, and potential long-term implications for their offspring. Furthermore, it will be important to examine cortisol levels in large samples of women in order to investigate any potential differences between ED sub-types. However, maternal cortisol levels during pregnancy is only one marker of HPA axis activity, and in order to gain a full understanding of the contribution of HPA axis activity during pregnancy on birth outcomes and infant development it will be important to investigate further biological markers. Furthermore, HPA axis activity during pregnancy is only one proposed mechanism that may contribute to birth outcomes in women with ED, and multiple systems are likely to be involved. Potential mechanisms that warrant further investigation in this area are, alterations in intrauterine blood flow, as well as the contribution of maternal nutrition during pregnancy and the interactions between these systems.

For the purpose of this thesis, it was only possible to follow-up a sub-sample of infant cortisol levels in the post-natal period. This investigation highlights that infants of women with ED during pregnancy might have an increased risk of elevated cortisol

levels. Given the potential long-term implication of this finding it will be crucial to follow-up the remainder of the mother-infant dyads in order to validate these findings. Future research is required to investigate the potential underlying mechanisms for elevated cortisol levels in infants of mothers with ED. Furthermore, it will be important to follow-up any potential implications for elevated cortisol levels, observed during early infancy in this sample, on their development later in childhood.

8.5 Clinical implications

The NICE (National Institute for Clinical Excellence, 2004) UK guideline for ED, suggests that increased ante- and post-natal support during pregnancy is required for women with ED. However, it is difficult to know the extent to which these guidelines are incorporated into routine care, since there is currently no available structured intervention for women with ED during pregnancy. Based on the findings of the investigations presented in this thesis, and previous evidence in this field of research, comprehensive guidelines for an evidence-based treatment for women with ED during pregnancy and in the post-natal period are proposed. Figure 8.1 depicts the key areas of risks for women with ED, prior to and during pregnancy, as well as in the post-natal period, with recommendations for the management of these potential risks.

8.5.1 The pre-conception period

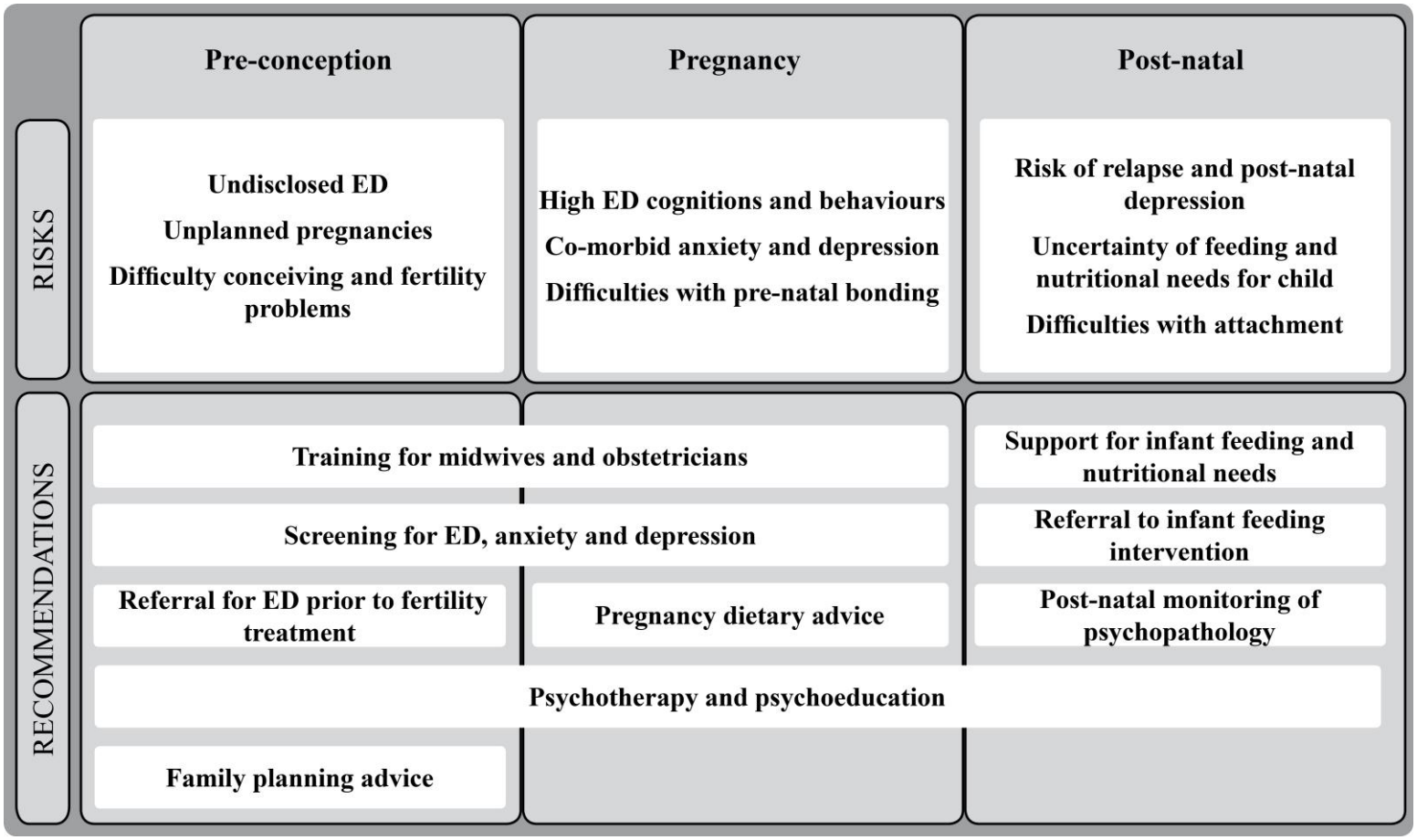
Findings from this thesis suggest women with ED may experience difficulties conceiving, and may therefore require additional support and advice prior to pregnancy; however the guidelines for fertility treatment of women with ED are presently unclear. NICE guidelines (National Institute for Clinical Excellence, 2004) currently suggest that a healthy BMI should be achieved prior to assisted reproduction, future guidelines should incorporate that specialist ED treatment should be provided for women who are experiencing difficulties conceiving who have a history of an ED, and ideally a reduction in symptoms should be achieved prior to conception.

Given the high prevalence of unplanned pregnancies in women with ED, particularly women with AN, women with ED may assume that they are unable to conceive and routine pre-conception advice and psycho-education should be provided by clinicians working with women with ED. Furthermore, it has previously been suggested that the oral contraceptive may not be an appropriate form of contraception for women who

regularly engage in SIV (Morgan, et al., 1999c), GP and family planning clinics should be made aware of these findings so as alternative methods can be discussed.

On the basis of previous evidence women with ED do not readily disclose their ED to healthcare professionals (Freizinger, et al., 2008), identification of women with ED is therefore a crucial factor in order for appropriate advice and treatment to be provided. Women's services, including ante-natal and fertility specialist, should routinely screen women for ED to ensure that appropriate help and support can be provided (Morgan, 1999a).

Figure 8.1: Recommendations for the management of eating disorders from pre-conception to the post-natal period



8.5.2 During pregnancy

As highlighted from the findings of this thesis, women with ED can continue to experience high levels of psychopathology during pregnancy. Nevertheless, given that ED symptoms have been found to reduce during pregnancy, it has been suggested that pregnancy may represent a period of increased motivation for women with ED and an optimal time for a target psychological intervention (Crow, et al., 2008). Support during pregnancy for women with ED, should primarily be aimed at reducing ED symptoms and behaviours, and prevention of relapse in the post-natal period. Given the high levels of anxiety and depression during pregnancy, and the implication for adverse birth outcomes, treatment of women with ED during pregnancy should also focus on the detection and reduction of anxiety and depression. Findings from this thesis suggest that treatment of anxiety during pregnancy for women with ED should not only focus on general anxieties but also pregnancy specific anxieties, which may be particularly high in women with ED during pregnancy.

Women with ED may experience problems adjusting to their pregnancy and experience difficulties with pre-natal bonding, therefore clinicians should be aware of this in order to assist transition to motherhood. Poor pre-natal bonding may be a risk factor for difficulties with attachment in the post-natal period, and therefore early intervention during pregnancy should be the preferred approach. Continuity of care for women with ED in the post-natal period is paramount. Women with ED have an increased risk of post-natal depression, and therefore monitoring of symptoms will be important and appropriate support and treatment provided.

8.5.3 Post-natal period

Increased levels of feeding difficulties have been identified during early infancy in mothers with ED, furthermore the present investigation highlighted differences in diet and growth in children of mothers with ED. Therefore, during the post-natal period women may need support to provide an adequate diet for their children, and regarding interactions around mealtimes, in order to facilitate appropriate growth and development. Previous interventions have been targeted at women with ED and their children, with promising results (Bryant-Waugh, et al., 2007; Stein, Woolley, Senior, et al., 2006). For example, Stein and colleagues (2006) developed a video feedback intervention targeted at improving mother-infant interaction in women with BN;

findings from a Randomised Control Trial into its effectiveness demonstrated that mealtime conflict and maternal eating psychopathology was markedly reduced in mothers receiving the intervention. Therefore, intervention targeted at women during pregnancy could be combined, where appropriate, with previous interventions targeted at mother and child in the post-natal period.

8.6 Concluding comments

In conclusion, the investigations undertaken in this thesis highlight several new findings regarding the effects of maternal ED on pregnancy and motherhood, and their children's development. Women with ED were found to experience difficulties in the pre-conception period and during pregnancy, which may have implication for the post-natal period. Furthermore, elevated cortisol levels during infancy were apparent in infants of women with active ED during pregnancy, and differences in the dietary patterns and growth trajectories of children of women with ED were highlighted. Several suggestions are made for future research, and ultimately for the support and treatment of women with ED during pregnancy and in the post-natal period.

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Appendix A

Further details of statistical modelling of growth trajectories used in Chapter 5 (Growth Trajectories in Children of Mothers with Eating Disorders) [12]

The standard way of modelling the relationship between a continuous outcome (in our example height, ponderal index (PI) and body mass index (BMI)) and a continuous exposure (in our example age) would be to fit a polynomial curve (i.e. age raised to the appropriate power). The patterns of growth across childhood, however, follow a complex pattern and may not be accurately represented by a simple polynomial curve. For this reason, we used fractional polynomials to find the best-fitting average height, PI and BMI trajectory for each of our models (height from birth to ten years, PI from birth to two years, BMI from two to ten years, separately for boys and girls).

Fractional polynomials is an approach to modelling the relationship between an outcome and one or more continuous covariates in which the continuous covariate is raised to a large number of combinations of powers, resulting in a wide range of possible curves and offering more flexibility than standard polynomial approaches (Royston and Altman 1994). In our example, age was raised to various combinations of powers, from which we selected the best fitting curve (the one with the lowest deviance). Individual random-effects allow intercepts and coefficients for each polynomial term to vary between individuals. Comparing actual versus predicted measurements showed the models to have good fit.

We also checked for auto-correlation (residual correlation between an individual's measurements as a decreasing function of the difference in the age at measurement, a phenomenon that can cause problems in growth models, particularly when repeated measurements are close together in time as they are in these analyses (Goldstein et al. 1994). We examined autocorrelation by computing the correlation between the difference between a measurement and the measurement predicted by the model (Predicted measurement$_n$ – measurement$_n$) and this difference for the previous measurement (Predicted measurement$_{n-1}$ - measurement$_{n-1}$). To verify that the models

[12] Prepared by Laura Howe for publication

were not dominated by individuals with large numbers of measurements, models were re-run with a random subsample of observations within each individual, such that no individual had more than the 75th centile number of measurements. The coefficients from these models were very similar to those from the full model, as were residual estimates for a given individual ($R \geq 0.9$).